# Implementation of Quality by Design (QbD) – Current Perspectives on Opportunities and Challenges

## Topic Introduction and ICH Update

*Advisory Committee for Pharmaceutical Science*
*and*
*Clinical Pharmacology*

*July 27, 2011*

**Moheb M. Nasr, Ph.D.**
**Office of New Drug Quality Assessment**
**OPS/CDER/FDA**

# Implementation of Quality by Design (QbD) Presentation Order

| | |
|---|---|
| • **Topic Introduction** | **Moheb M. Nasr, FDA** |
| • **Industry Perspective** | **Gerry Migliaccio, Pfizer** |
| • **Industry Perspective** | **Yatindra Joshi, Teva** |
| • **Regulatory Perspective** | **Evdokia Korakianiti, EMA** |
| • **Regulatory Perspective** | **Sarah Pope-Miksinski, FDA** |

# Topic Introduction and ICH Update

- ICH guidelines, Quality by Design (QbD), and recent ICH activities
- ICH implementation progress
- Remaining challenges and gaps
- Industry and regulatory perspectives
- Questions to ACPS-CP

# ICH Q8 (R2) Pharmaceutical Development

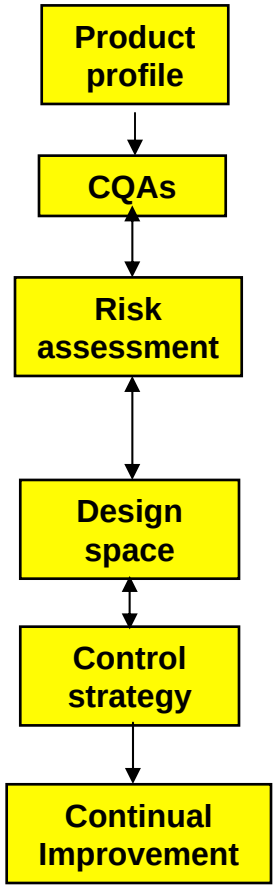
- Describes good practices for pharmaceutical product development
  - Outlines basic and enhanced (QbD) development and manufacturing approaches
  - Introduces concepts of design space and flexible regulatory approaches

# What is Quality by Design (QbD)?

- Systematic approach to development
- Begins with predefined objectives
- Emphasizes product and process understanding and process control
- Based on sound science and quality risk management

*from ICH Q8(R2)*

# Example QbD Approach - Q8(R2)

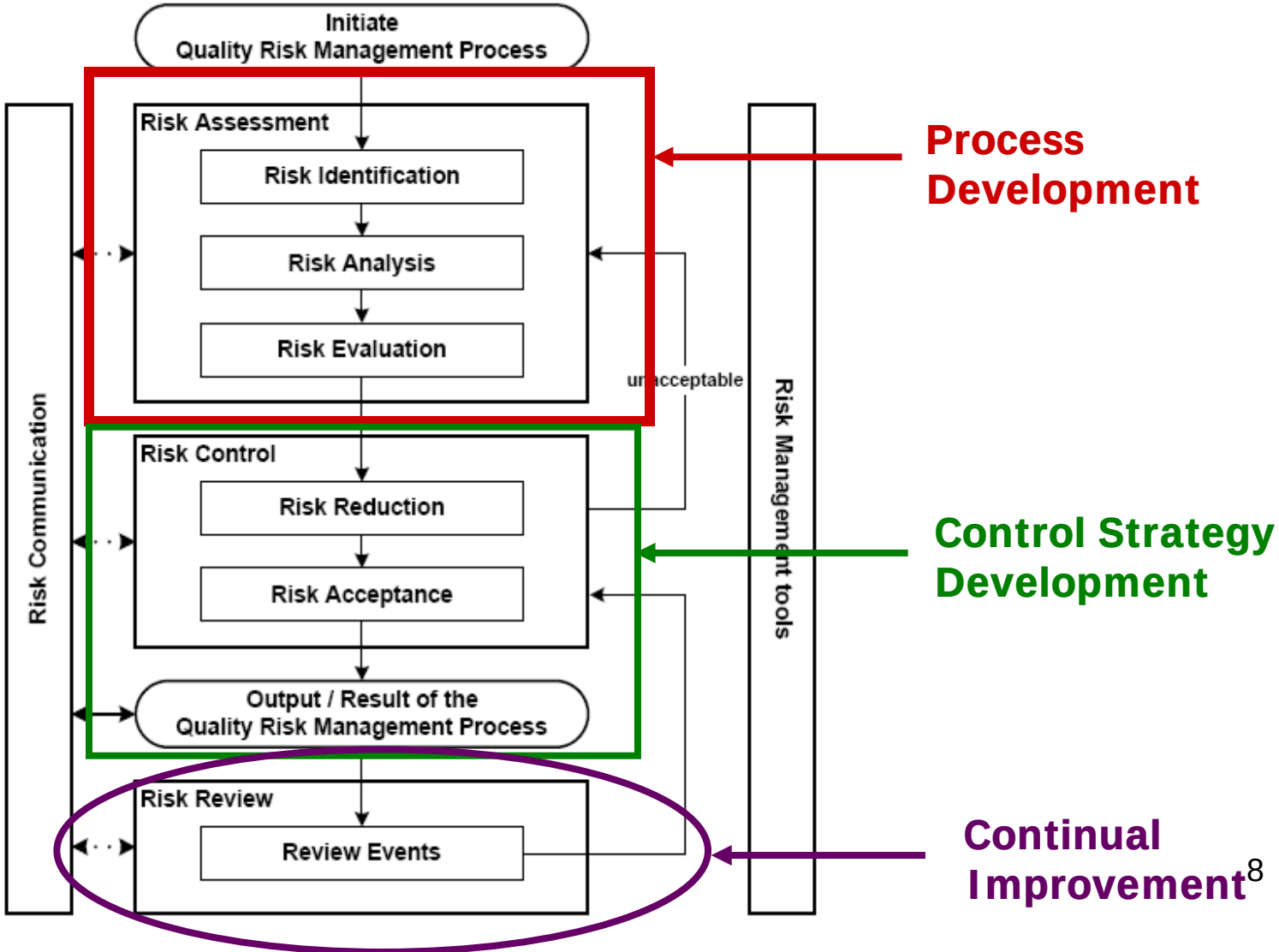



- Quality Target product profile (QTPP)
- Determine critical quality attributes (CQAs)
- Link raw material attributes and process parameters to CQAs and perform risk assessment
- Develop a design space
- Design and implement a control strategy
- Manage product lifecycle, including continual improvement

# ICH Q9 - Quality Risk Management

- Describes a systematic process for the assessment, control, communication and review of quality risks
- Includes principles and examples of tools for quality risk management (QRM)
- Applies over product lifecycle: development, manufacturing and distribution

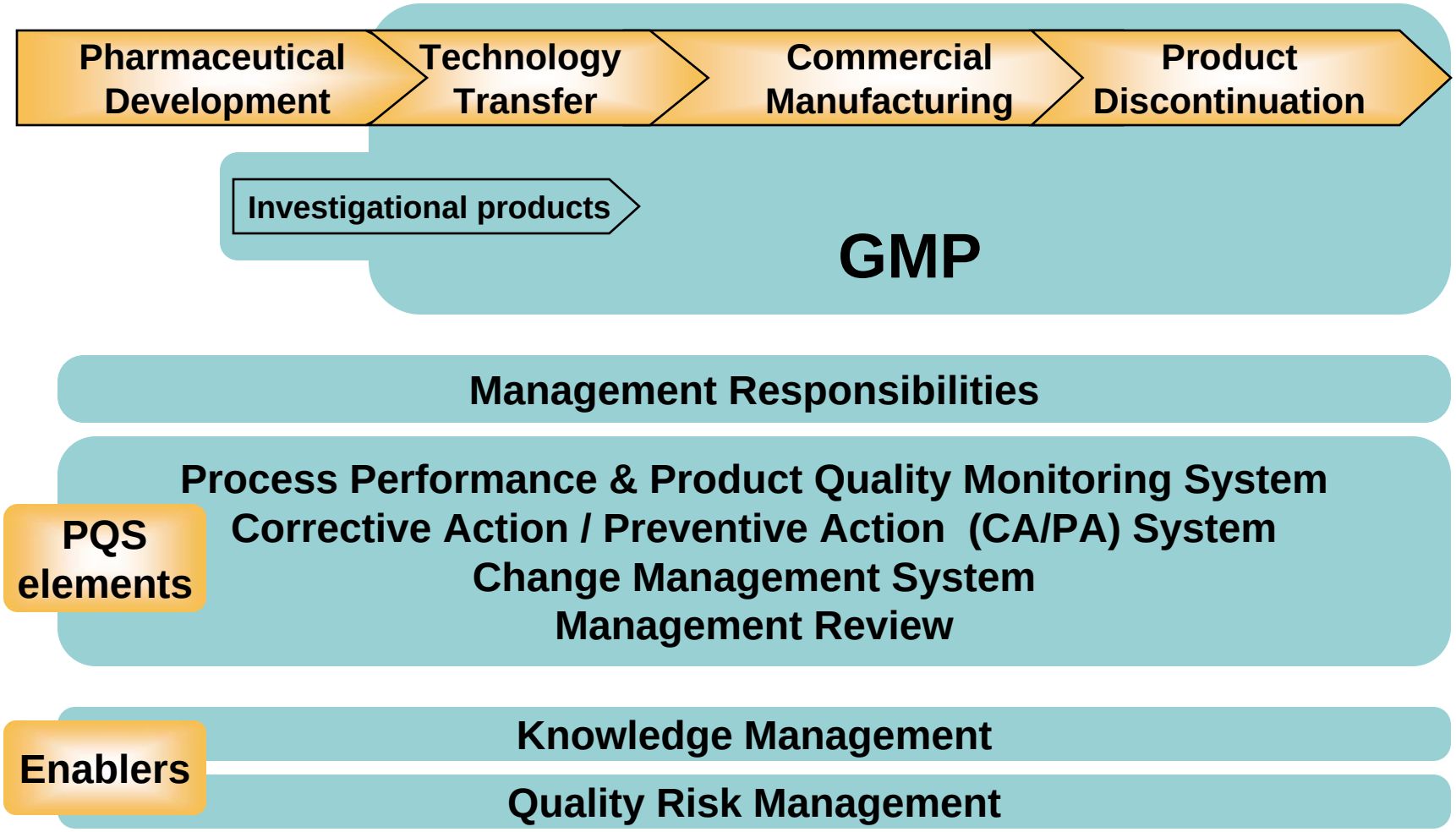
# ICH Q9 – Quality Risk Management Process



# ICH Q10 - Pharmaceutical Quality Systems

- Describes systems that facilitate establishment and maintainence of a state of control for process performance and product quality
- Facilitates continual improvement
- Applies to drug substance and drug product throughout product lifecycle

# Pharmaceutical Quality System (PQS) – Q10



# Demystification of QbD (1)

- QbD is a systematic approach to pharmaceutical development and manufacturing using:
  - Modern scientific and quality risk management (QRM) principles
  - Quality control strategies based on product and process understanding
- Sufficient details of development and manufacturing information to be included in regulatory submissions
- Regulatory decisions must be based on scientific and QRM principles

# Demystification of QbD (2)

- QbD doesn't equal Design Space (DS) and/or Design of Experiments (DOEs)
- DS is not required, but establishing a DS is useful to show product and process understanding and to provide manufacturing and regulatory flexibility
- Public standards continue to have a role but some adaptation is needed
- QbD doesn't have to be expensive
  - It can reduce manufacturing and regulatory cost

# Demystification of QbD (3)

- QbD doesn't change/reduce regulatory requirements
  - Opportunities for flexible regulatory approaches
- QbD is important for all products including generics and biotech
- Analytical testing is important and play a key role in the QbD (development and implementation)
- End product testing is a component of the control strategy
  - Bioavailability and bioequivalence need to be demonstrated by dissolution testing and/or other means

# The Utility of ICH Q8, 9 &10

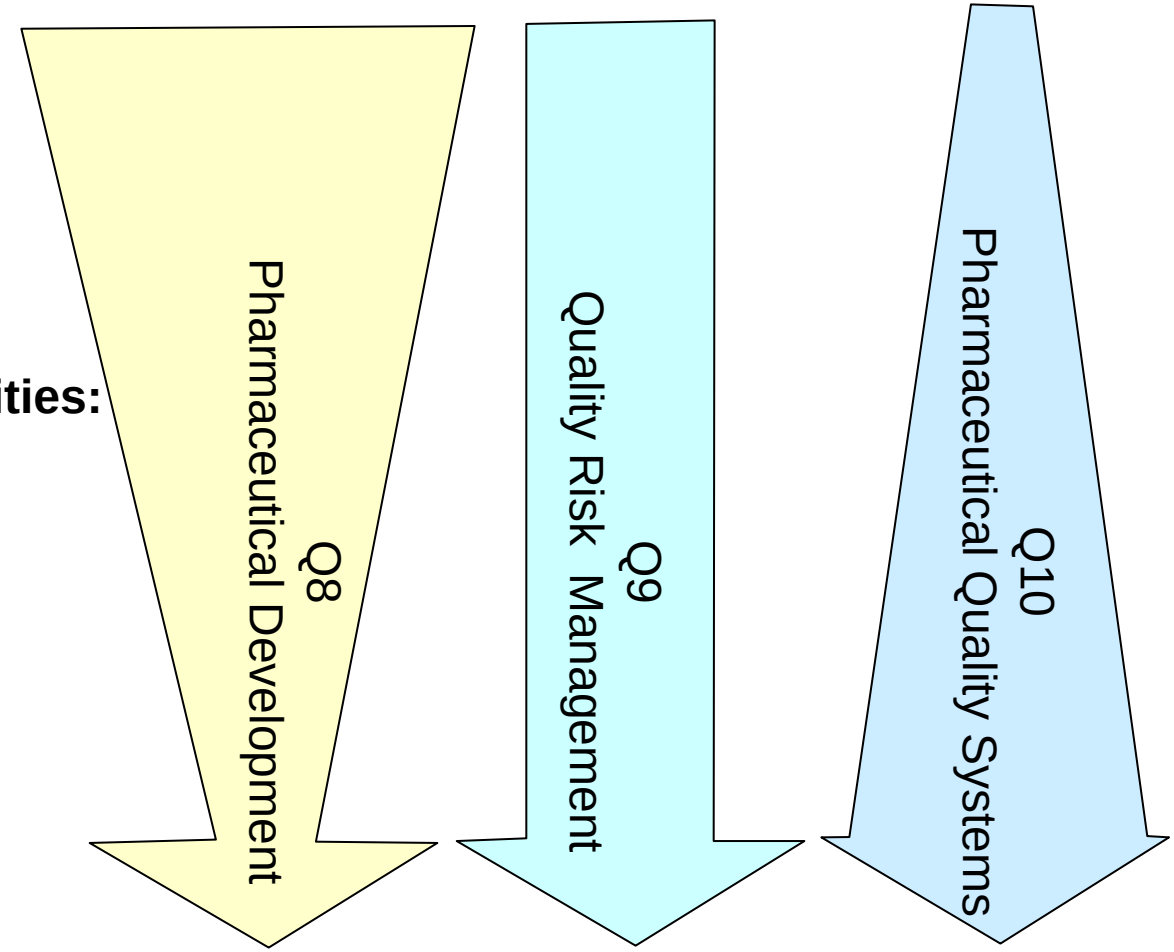
- The implementation of Q8, 9 &10 is valuable for all drug products, pharmaceutical development approaches and regulatory systems:
  - Simple and complex dosage forms
  - Small molecule and biotech
  - Traditional development and QbD
  - Within and outside ICH regions
- Good scientific development (Q8) in combination with QRM (Q9) and PQS (Q10) will improve drug quality and efficiency of pharmaceutical manufacturing
  - Quality is important for all drug products throughout product lifecycle (new, legacy and generics)

# ICH Q8, Q9 and Q10 Working Together

**Formulation Activities:**
- QTPP Definition
- Pre-Formulation Studies
- Formulation Screening
- Optimization & Selection

**Process Development Activities:**
- Process Screening
- Lab Scale Development
- Scale-Up Studies

**Manufacturing Activities:**
- Commercial Scale Manufacturing
- Batch Release
- Continual Verification & Improvement



# IWG: Implementation of Q8, Q9 and Q10

- Scope: ensuring harmonized implementation
- Identified areas needing further clarification
  - Knowledge Management, Design Space, Real Time Release, Control Strategy and Pharmaceutical Quality System
- Activities include: Publication of Q&A, Training, Collaboration with other organizations
- Comments and questions access from ICH website www.ich.org, Quality-Guidelines-menu, under Q8, Q9 and Q10

# ICH – Q-IWG Achievements Summary

- Published 45 Q&As
- ICH Training
  - Developed extensive training materials
  - Workshop results compiled and evaluated
- Identified several topics for potential collaboration with outside organizations
- Evaluated the influence on the existing ICH Q-Guidelines
- Developed points to consider documents

# IWG: Implementation of Q8, Q9 and Q10

- Training has been a major achievement of Q-IWG
  - ICH regions:
    - EU: Tallinn — June 2-4, 2010
    - US: Washington — October 6-8, 2010
    - Jpn: Tokyo — October 25-27, 2010
  - ASEAN, Kuala Lumpur — July 2010
  - IFPMA/DIA, Seoul — April 2011
  - HC, Ottawa — September 2011
  - APEC/AHC, Seoul — October 2011
- Training material available at ICH website
  - **http://www.ich.org/products/guidelines/quality/training-programme-for-q8q9q10.html**

# Training Materials

- **A comprehensive case study (API and DP) was developed**
  - Case study and A/V presentation available on ICH website
- **5 plenary presentations covering**
  - Interrelationship of Q8, Q9 & Q10
  - Development
  - Assessment
  - Manufacturing implementation
  - Inspection
- **Training outline and key messages for four topics:**
  - Design Space (DS), Control Strategy (CS), Pharmaceutical Quality System (PQS) & Quality Risk Management (QRM)

# Key Messages (1)

- ICH Q8, Q9 and Q10 are linked together to provide a systematic, modern risk- and science- based approach to pharmaceutical manufacturing and development
- Comprehensive implementation of the three guidelines together is essential to achieve ICH Quality Vision
  - Guidelines are applicable over entire product lifecycle
- Guidelines can be utilized by all stakeholders
  - Industry and regulators
  - Assessors and inspectors are expected to incorporate QRM during regulatory processes

# Key Messages (2)

- Traditional development approaches, as outlined in ICH Q8(R2) part I, are acceptable
  - Enhanced approaches (QbD) provide higher assurance of product quality and additional opportunities for manufacturing efficiency and flexibility
- The use of quality risk management (methodologies and tools - Q9) is beneficial regardless of development or manufacturing approaches used
- Pharmaceutical Quality Systems (Q10) applies to drug substance and drug product throughout product lifecycle and provide tools to facilitates continual improvement

# Summary Findings from ICH Workshops

- New paradigm not yet fully implemented
  - Remaining concern about the cost and potential impact of time to market
- Lack of global harmonization (especially outside ICH region) could have a negative impact on future implementation of Q8, 9 & 10
  - Impact of different change management regulatory processes over the life cycle of the product
- There is a training need for regulators and industry
- Need for appropriate continuous dialogue between industry and regulators (inspectors & assessors) before, during & after assessment

# ICH IWG – Current Activities and Next Steps

- Development of implementation documents ('Points to Consider') to address 6 remaining technical and regulatory gaps
  - Completed June 16, 2011
    - Level of Documentation in Enhanced (QbD) Submissions
    - Criticality of Quality Attributes and Process Parameters
    - Control Strategy
  - To be completed by end of 2011
    - Process validation
    - Design Space
    - Role of Modelling in QbD

# Points to Consider (1)

- The ‘Points to Consider’ are based on questions raised during the ICH Q-IWG training workshop sessions in the 3 regions
- The points to consider are not intended to be new guidelines and/or to introduce new or increased regulatory requirements.
  - They are intended to provide clarity to both industry and regulators and to facilitate the preparation, assessment and inspection related to applications filed for marketing authorizations.

# Points to Consider (2)

- The development approach should be adapted based on the complexity and specificity of product and process
  - Applicants are encouraged to contact regulatory authorities regarding questions related to specific information to be included in their application.
- Using Quality by Design (QbD) approach does not change regional regulatory requirements but can provide opportunities for more flexible approaches to meet these requirements
  - In all cases, GMP compliance is expected.

# Criticality of Quality Attributes and Process Parameters

- Considerations for Establishing CQAs and CPPs
- Relationship between Criticality and Control Strategy

# Control Strategy

- Life-cycle of the control strategy
- Suitability of control strategy at different scales
- Specifications and Certificate of Analysis (CoA) for Real Time Release Testing (RTRT)
- Process for a batch release decision

# Level of Documentation in Enhanced (QbD) Regulatory Submissions

- Risk Management Methodologies
- Design of Experiments
- Manufacturing Process Description
- *Role of Modeling in QbD and Design Space will be developed next*

# ICH SC Endorsements (June 16, 2011)

- ‘Points to Consider’ document was endorsed
  - Criticality of Quality Attributes and Process Parameters
  - Control Strategy
  - Level of Documentation in enhanced (QbD) Regulatory Submissions
- ‘Points to Consider’ document to be developed
  - Process validation/process verification
  - Role of modeling in QbD
  - Design space
- IWG work to be completed by end of 2011

# Current Challenges

It is important to note that QbD didn't and was not expected to solve ALL pre-QbD quality challenges.

# Current Challenges (1)

- Lack of clarity of regulatory expectations
  - Partially addressed by Q-IWG
- Reluctance to share information in regulatory submissions
  - Detailed scientific justification of control strategy
- Control strategy
  - Linkage between control strategy and pharmaceutical development, PQS and GMPs
  - Evolution of control strategy throughout the product life cycle

# Current Challenges (2)

- Adoption of a Risk-based approach to CMC review
  - What is needed for approval decision vs. “nice to know” for scientific understanding
- Change management
  - Robustness of internal processes for all changes (not only those requiring regulatory notification)
- Role of reviewer and inspector/investigator
  - What to be submitted and what to evaluate during inspection
  - What, if any, PQS information should be included in the application

# ACPS-CP Questions
# July 27, 2011
# Implementation of Quality by Design (QbD) – Current Perspectives on Opportunities and Challenges

1. Are there additional efforts the FDA should consider in order to facilitate the implementation of Quality by Design (QbD)?
2. How should we address the technical and regulatory gaps that have been identified by the speakers?
3. Can QbD approaches be valuable for biotechnology product development? If so, are there any potential scientific challenges that we should be aware of?

# The Impact of Quality by Design (QbD) on Manufacturing and Product Quality - Innovator Industry Perspective

FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology
July 27, 2011

Gerry Migliaccio
Senior Vice President, Network Performance
Pfizer Global Supply

# The Journey to Operational Excellence is Enabled by Quality by Design

| | Six Sigma | Lean | IbM |
|---|---|---|---|
| Goal | Improve Process Capability | Reduce Waste | Optimize Performance |
| Approach | Method 1, 2 & 3 | Method 4 | Predictive & Adaptive Tools/Knowledge Eng |
| Benefit | Reduced Variability<br>Reduced Defects<br>Improved Process Control | Reduced lead Time<br>Lower Inventory<br>Higher utilization rate | Improved Cost/Efficiency<br>Increased Capacity<br>Improved capability due to Adaptive process control |

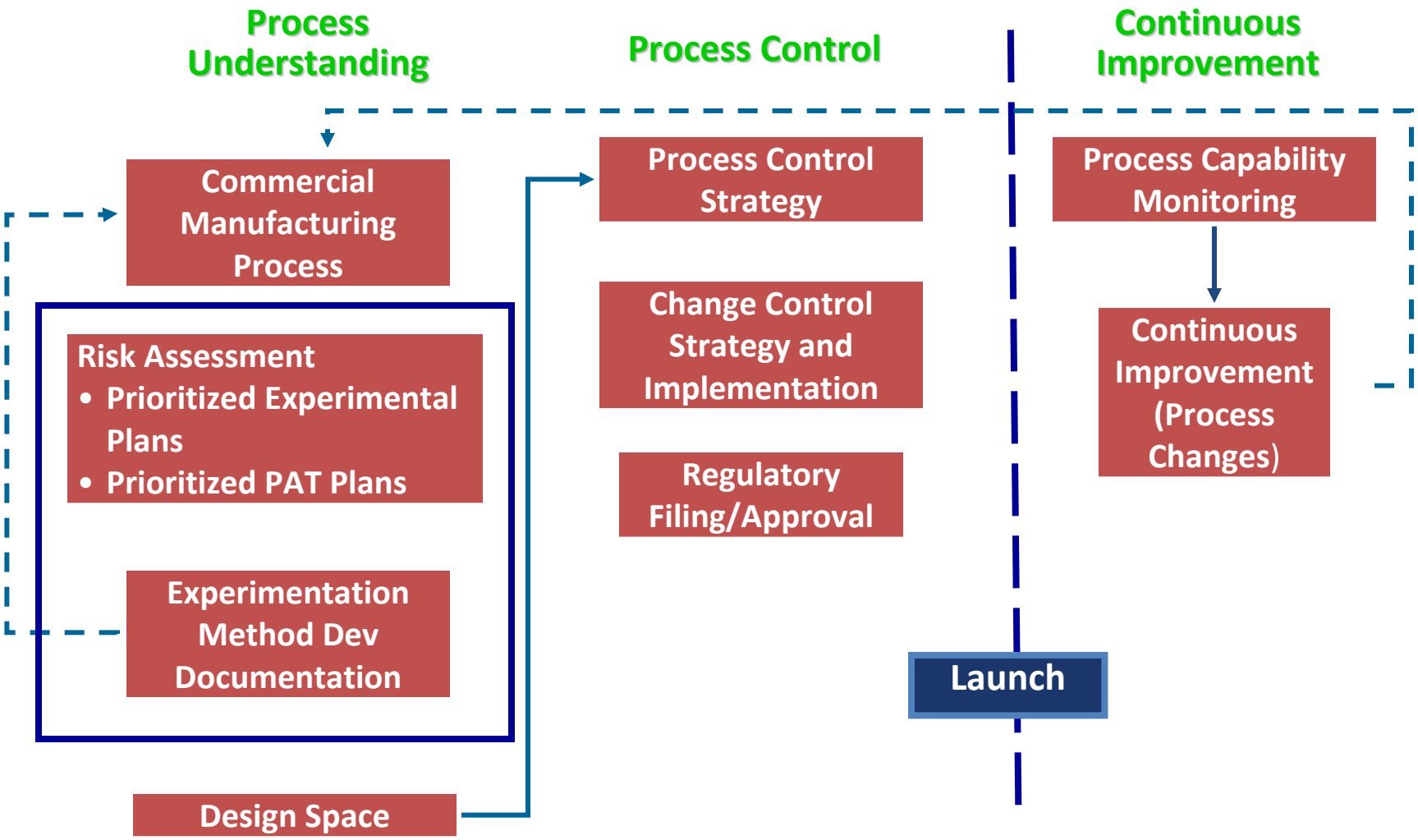
**IbM = Intelligence Based Manufacturing**

# Demonstrated Benefits of QbD

- **Enhanced Process Understanding**
- **Higher Process Capability**
- **Better Product Quality**
- **Increased Flexibility to Implement Continuous Improvement Changes**
- **Value!**

**Note that much of the QbD investment occurs in process development, and the benefit is realized in commercial manufacturing**

# Quality by Design



# Elements of QbD at Pfizer (1)

- **Quality Target Product Profile**
  - **Product designed to meet patient needs**
- **Understand physical, chemical, microbiological and biological properties of materials that may impact product quality or process performance**
  - **Compendial specifications may not be adequate**
- **Risk Assessments**
  - **Prior knowledge, data mining**
  - **Process mapping**
  - **Inputs (x) >> Outputs (y)**

# Elements of QbD at Pfizer (2)

- **Experimental Plans**
  - **Understand y = f(x)**
  - **Multifactorial, multivariate**
  - **Modeling – predictive, statistical, simulations**
- **Risk Mitigation**
- **Understand Criticality**
- **Develop Design Space**
- **Establish Control Strategy**
- **Knowledge Management**
- **Continuous Improvement**

# Enhanced Process Understanding

## Process Understanding Plan (PUP)

Assessment included **7 Focus Areas** with

- 52 Attributes
- 190 Parameter

**(1st Pfizer QbD Product)**

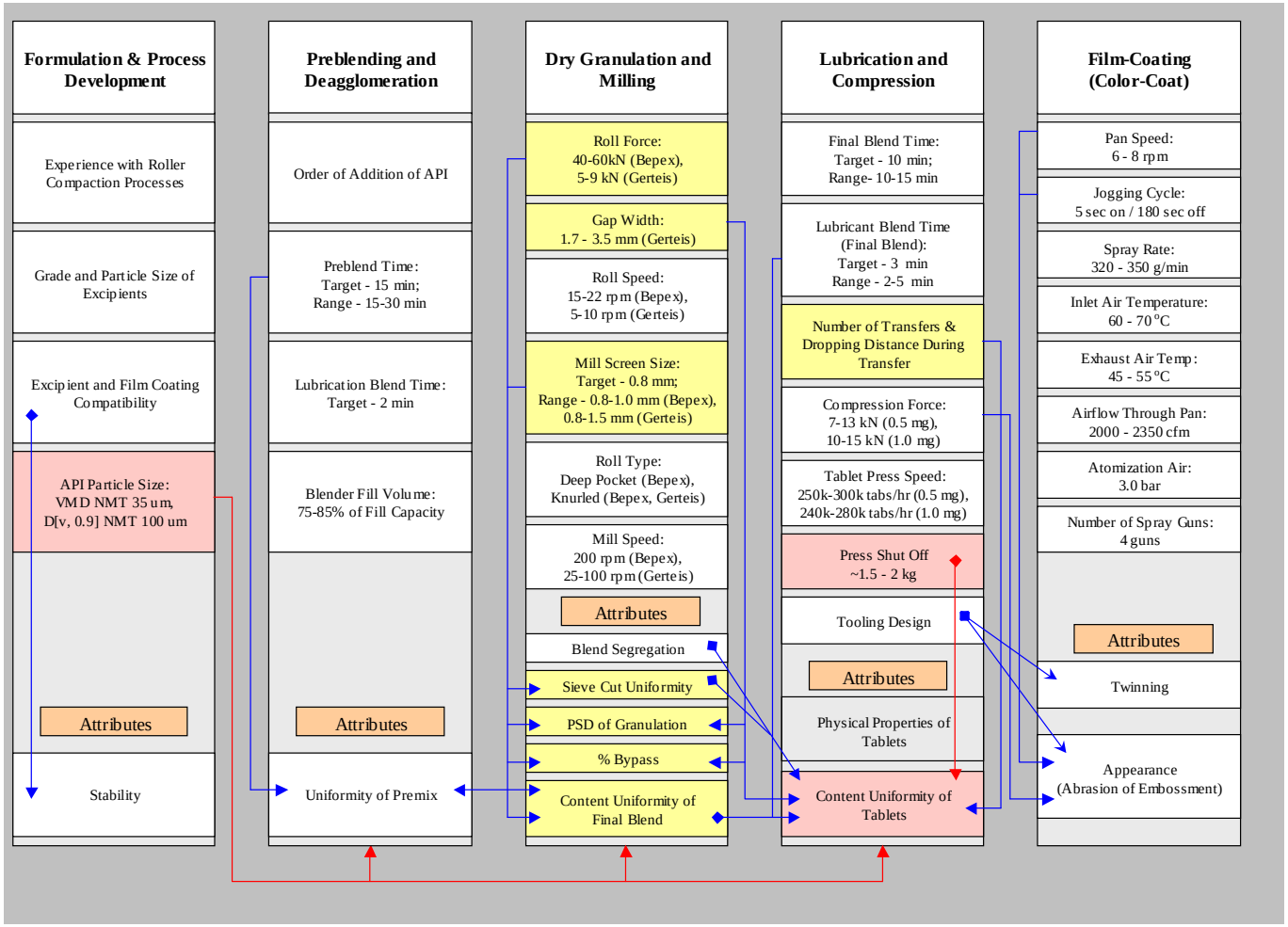
Experimental strategy

➔ Knowledge PUP

**Design Space**

**Knowledge / capability**

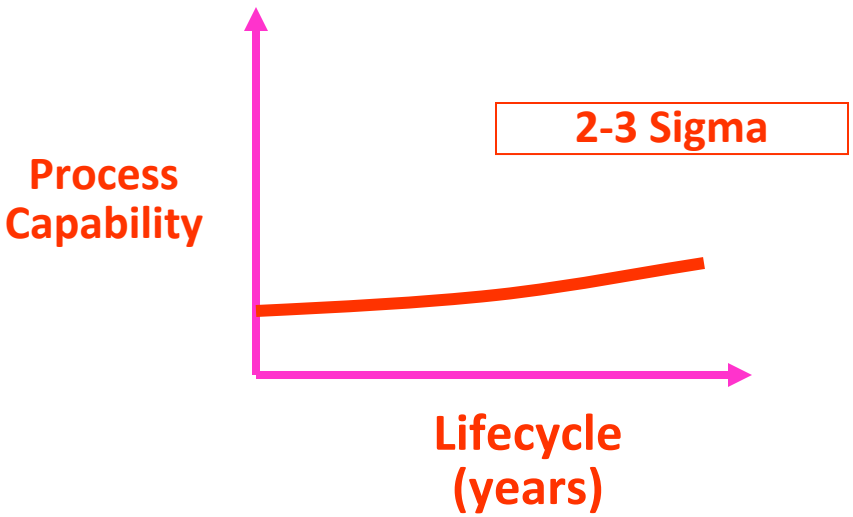
# Enhanced Process Understanding



# Higher Process Capability and Product Quality

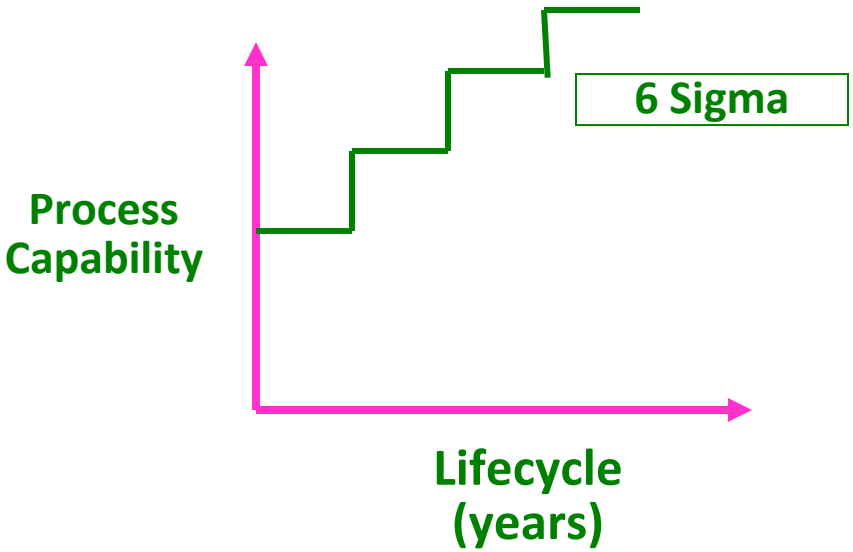
**Traditional Approach**

**Fixed Process**




**QbD Approach**

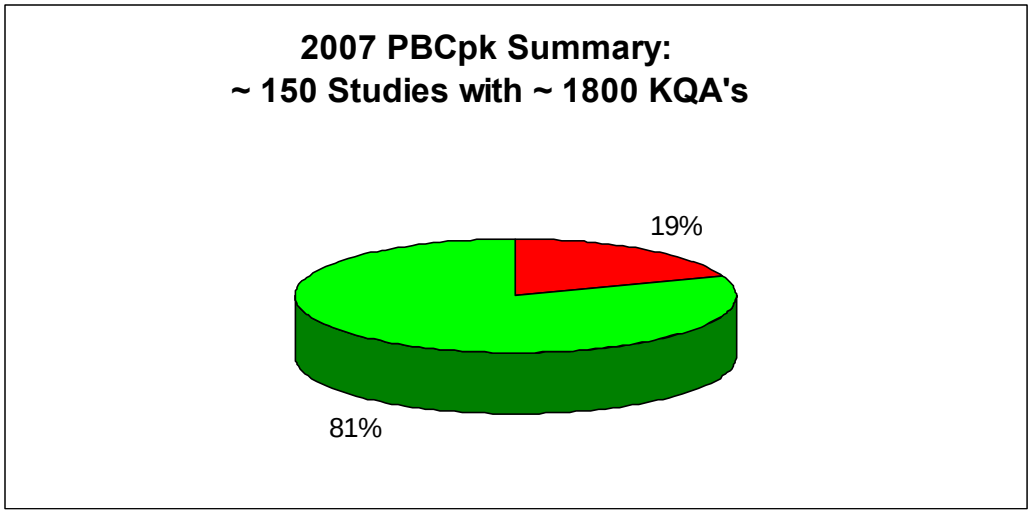
**Continuous Improvement**

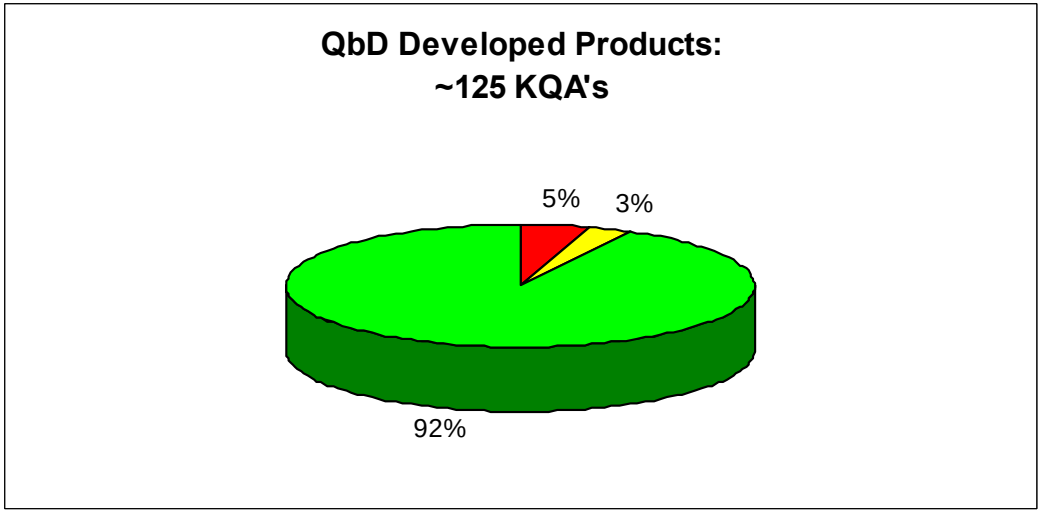


# Higher Process Capability

Traditional

QbD




**Red <1 PBCpk**

**Green >1 PBCpk**

# Higher Process Capability

**Quality by Design results in a robust process and enables rapid improvements in process capability**

**1st Pfizer QbD Product**

**Assay PpK at launch = 1.2 (3-4σ)**
**Ppk 6 months post-launch = 1.8 (5-6σ)**

# Better Product Quality

**2007 deviation rates for three tablet products manufactured in same facility**

| Product | Year Launched | % Batches with Deviation in 2007 |
|---|---|---|
| A (2 strengths) | 1991 | 4 – 8% |
| B (2 strengths) | 1992 | 0 – 1.5% |
| C (1 strength) | 2007 | 0.7% |

Traditional w/CI

QbD

**QbD resulted in lower deviation rate in the 1st year after launch than achieved through traditional continuous improvement efforts.**

# Increased Flexibility

- **Demand for 1st QbD product was 4X forecast**
- **Due to well-developed design space, site was able to increase productivity by 66% by optimizing process parameters within design space – no regulatory filing required.**
- **Further improvements were made by expanding the design space with appropriate regulatory submissions.**

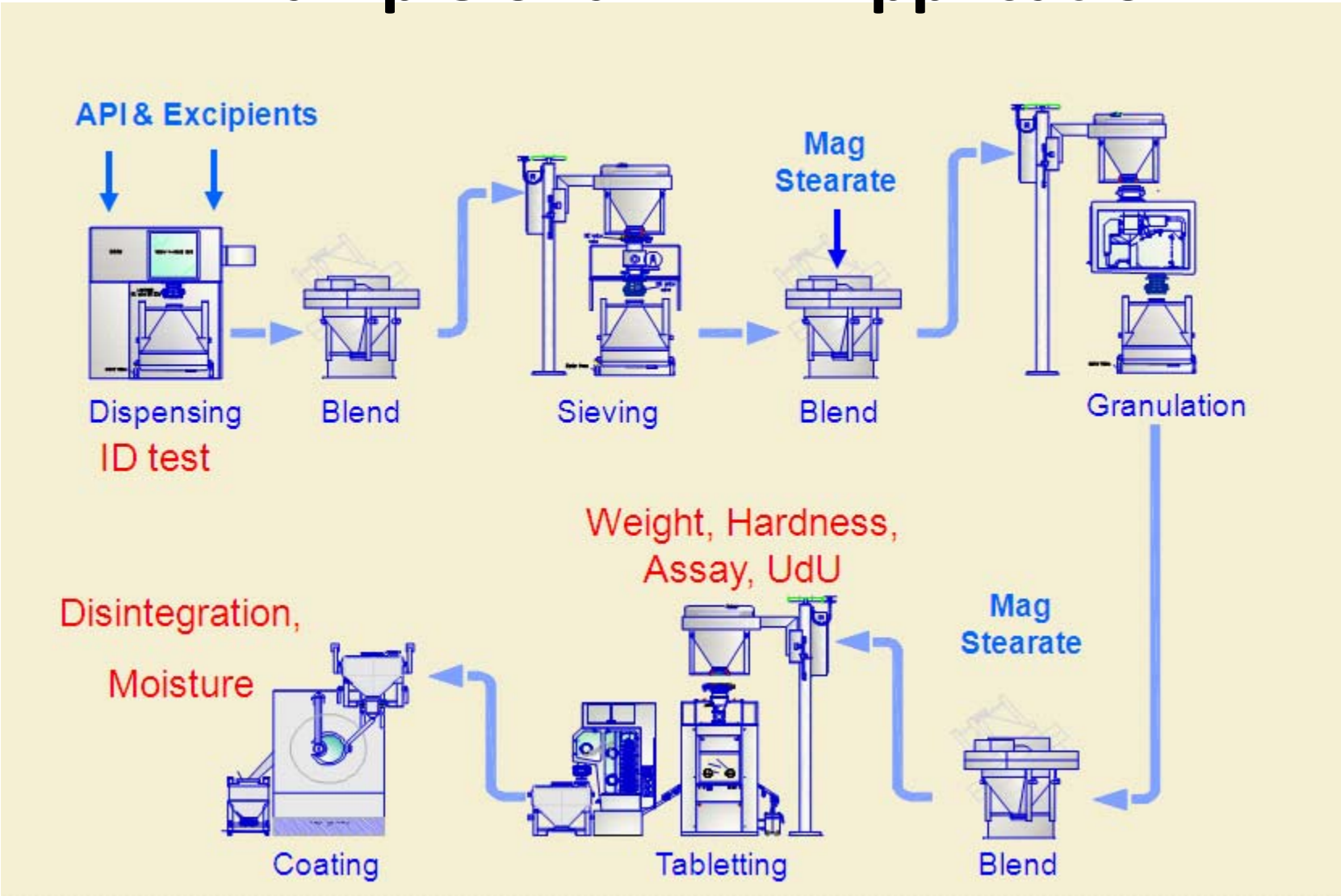
# The QbD Value Proposition

- **Product/Process design**
  - **"Lean by Design" equals $$$**
- **Process/Product robustness**
  - **Reduce defects, rejections, investigations**
- **Process control**
  - **Reduce testing, inventory costs**
  - **Improved yields, Cost of Goods**
- **Regulatory flexibility (QbD Filing)**
  - **Continuous improvement**
- **But where do we go from here ??**

# Real Time Release

- Shift of analytical control from an off-line, post-manufacturing approach to an approach where data is generated during manufacturing.
- RTR does not mean less testing, in fact it often means more analytical data is generated!
- Provides for control closer to the source of variability in the process.
- Allows for Real Time Release of the batch.
- Regulators have already demonstrated their willingness to review and approve RTR submissions.

# Example of an RTR Application



# The RTR Value Proposition

- **Reduced QC Lab costs**
- **Reduced through put time**
  - **Reduced inventory**
- **Experience to date indicates pay-back time of ~ 12 months**
  - **Dependant on product volume**
  - **Dependant on required upfront investment**
  - **Dependant on inventory value**

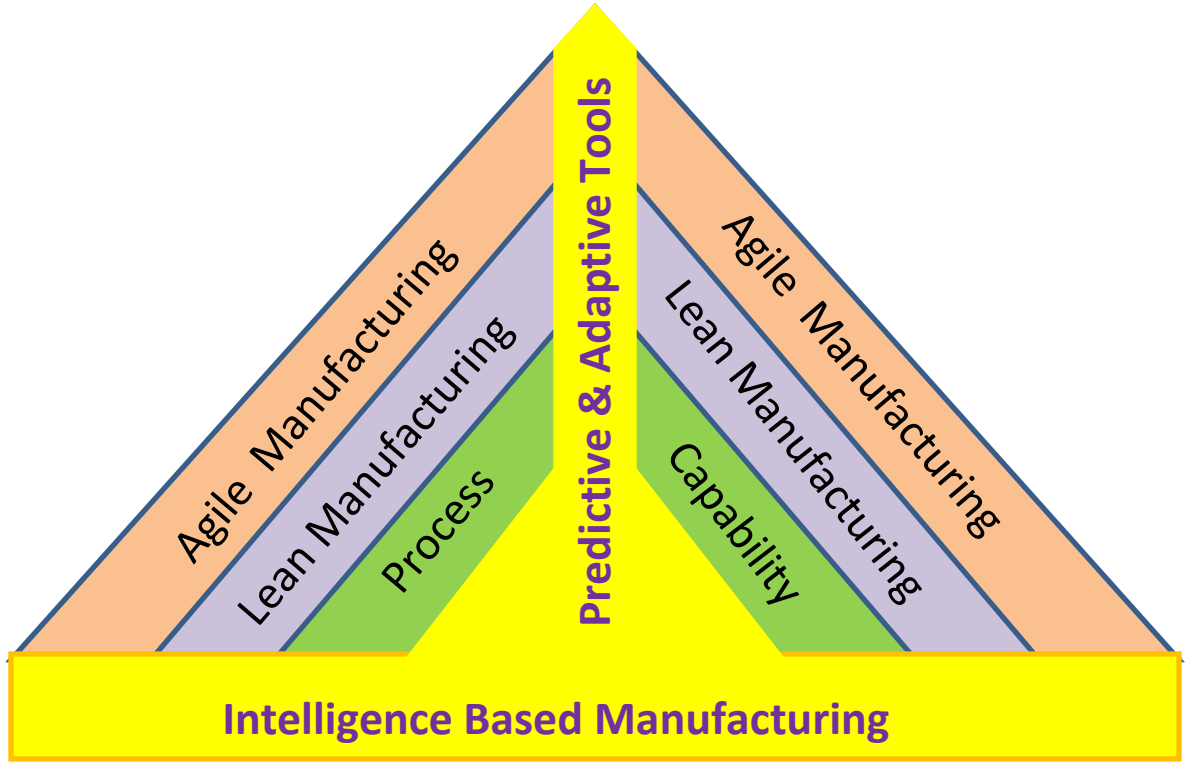
# Use of Large Sample Sets (Large N)

- New control strategies allow for significantly larger sample sizes than traditional compendial testing
- Modified approaches are required to treat this data, especially for uniformity testing
- zero tolerance criteria no longer make sense
- Pharma paper in 2006 (Sandell, et. al.)
- FDA and EDQM teams continue discussions

# QbD Applied to Existing Products

- **Process redesign**
- **Partial design spaces**
- **Enhanced control strategies (including RTR)**
- **Enhanced process understanding**
- **New technologies such as continuous manufacturing**

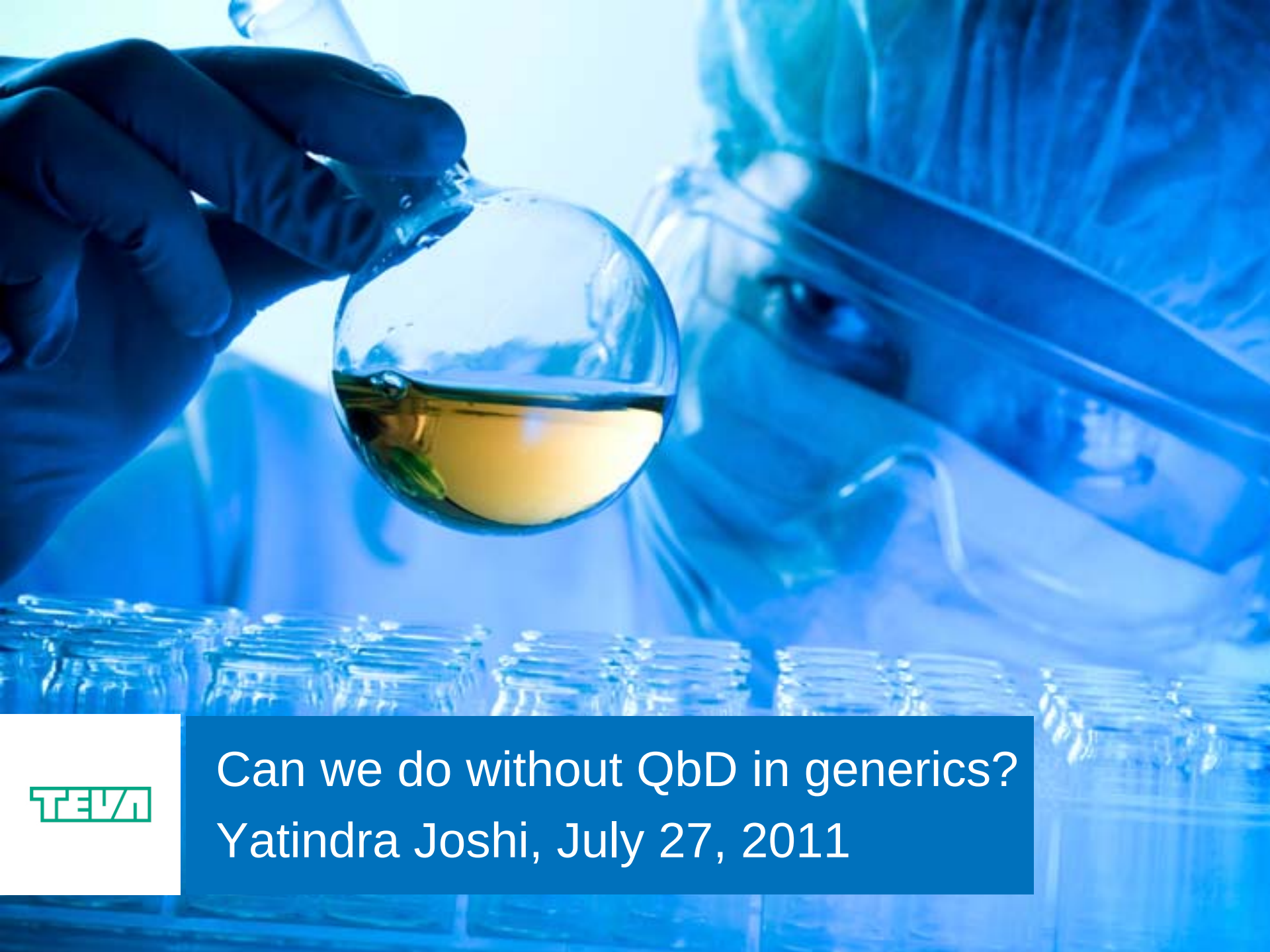
# Intelligence Based Manufacturing
# aka Adaptive Processes




Predictive & Adaptive Models reduce the impact of variability and uncertainty on process outcomes

# Conclusions

- Quality by Design works!
- It is here to stay …….
- Future opportunities await



# Can we do without QbD in generics?

Yatindra Joshi, July 27, 2011

# Disclaimer

*Views presented herein are based on my interactions with my counterparts from other companies and not necessarily those of Teva Pharmaceuticals.*

# Questions to ask ourselves…

*…Can we do without QbD in generics?*

*Do we want to get it right the first time every time?...*

*…How do we find the balance between speed and excellence?*

*By applying science efficiently and utilizing our prior knowledge effectively…*

# A few key points to consider……

- Affordability of healthcare is important to all of us.
- Generic companies are making medicine affordable.
- Seven of every ten prescriptions (~72%) in the US are filled with generic products, and therefore, uninterrupted supply of medication is in the best interest of the industry as well as our patients.
- We need to continue to make quality medicine available and affordable?

# A few points to consider…

- **Is QbD the only way to make quality products?**
  - Some will say: Definitely not!
    - ✓ Has the generic industry not provided quality products for many years?
    - ✓ Could the industry attain 72% market share without quality products?
    - ✓ Are the quality issues faced by generic companies any different from those faced by the brand companies?
  - Are there supply interruptions?
    - ✓ Product on short supply.

# McKinsey Report (Fuhr, Holcomb, Rutten)

- Why QBD should be on the executive team's agenda?
  - Product and Process Development (PPD) – API, formulation, analytical, process development, validation, and preparation for commercial manufacture account for 15-30% of overall R&D expenditure.
    - ✓ Ineffective PPD is costing companies up to 20% of potential profits.
    - ✓ For the industry as a whole, PPD could represent an incremental $20-30 billion in profits
    - ✓ PPD can increase an individual compound's lifetime value by 30-50%.

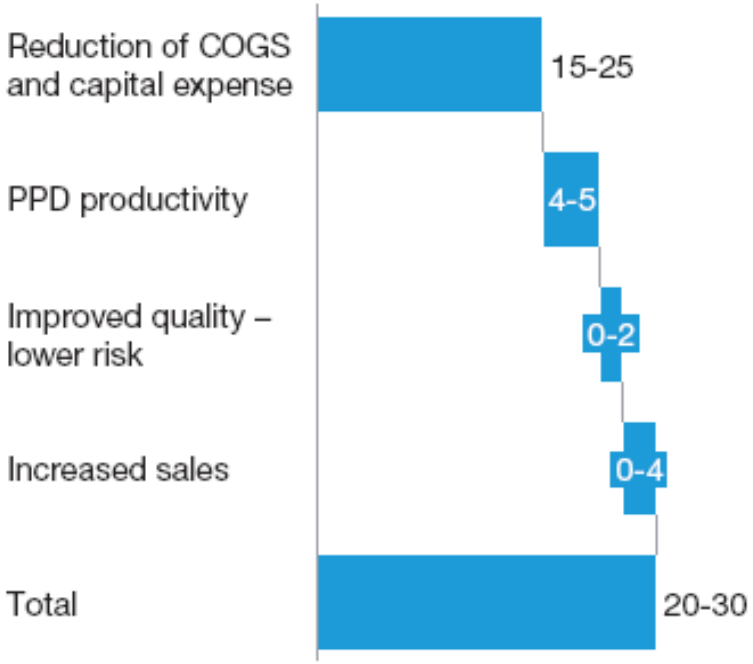
# “Why QbD should be on the executive’s team agenda”,

Ted Fuhr, Michele Holcomb, Paul Rutten; McKinsey

exhibit 2

$ Billions

**Sources of incremental annual value**




**Description**

- Savings primarily through cycle time, yield and quality improvement
- Savings through use of QbD techniques in product development
- Potential savings due to reduced risk of regulatory citation (e.g., 483, warning letter)
- Potential revenue growth through better launches and improved product design

Note: Pharmaceutical industry COGS estimated $145-166 B, PPD spend estimated $15-17 B
SOURCE: McKinsey

# “Why QbD should be on the executive’s team agenda”,

Ted Fuhr, Michele Holcomb, Paul Rutten; McKinsey

*…Organizations that embrace PPD can significantly reduce costs, improve products, shorten time to launch, reduce risk, and improve patient benefits…*

# Levels of Adoption of QbD Among Companies

**Exhibit 3: Level of maturity and drug type of examined companies**

| Group | Novice | Pilot | Rollout | Fully implemented | Total |
|---|---|---|---|---|---|
| New Drug | 22% | 33% | 22% | 22% | 100% |
| Gx | 40% | 20% | 40% | -- | 100% |
| Biologics | 17% | 67% | 17% | -- | 100% |

"Understanding Challenges to Quality by Design", FDA, 2009

# Questions to ask ourselves…

*…If QbD (PPD) can indeed be beneficial to the industry as pointed out by McKinsey, why is the QbD implementation not complete and why is there so much concern (or skepticism)?…*

# A few points to consider…

- **Challenges in adoption of QbD?**
  - Using past success to predict the future.
  - We are doing just fine – no thanks.
  - Resistance to the change, “who moved my cheese” syndrome.
  - Difficulty to see the long term benefit and business-case.
  - QbD will slow us down and will impact ability to achieve FTF?
  - QbD will increase our development cost significantly.
  - The more we will tell the FDA, the more questions we will have, and more difficult it will be to gain approval.
  - Will the review be consistent from one application to another and from one reviewer to another?

# Direction of the Generics Industry….

*…Despite the adoption challenges, it is clear to the Generics Industry that not implementing QbD is not an option…*

# Future direction…

## *…Can we do without QbD in generics?*

*We do want to get it right the first time every time…*

*We do want to reduce cost, shorten time to approval and launch, and provide uninterrupted supply of high quality and affordable medication to our patients…*

*OGD has made it clear to the industry that not implementing QbD is not an option…*

# What has OGD done well?

- Partnered with GPhA and several companies in the industry to develop QbD guideline.
- Held several meetings with the industry to:
  - Reported work in progress
  - Got industry perspective
  - Organized workshops on key topics and reported results
  - Provided clear directions
  - Developed guidelines
  - Made Design Space and PAT optional

# …How do we apply QbD in generics?…

- Race to "First to File".
- Frequently limited amount of API and the need to go to pivotal.
- A balance between what parameters to fix and what to keep variable.
- A balance between what to do before and what to do after submission.
- A balance between risk and opportunity.
- A balance between risk and budget

# Gaining Efficiency with Systematic Development

- **Build your development strategy** prior to any development work based on predefined objectives and risk assessment :
  - ✓ Define your Development Goal:
    - What do you want to make?
    - How do you want to make it?
    - What manufacturing site do you want to make it in?
    - What equipment and expertise will be needed?
      - Understanding of the molecule
      - RLD Characterization
      - API Characterization
      - QTPP Justification
      - CQAs Justification

**A lot of information is already available for generics**

# Gaining Efficiency with Systematic Development

- **Build your development strategy** prior to any development work based on predefined objectives and risk assessment (cont.) :
  - ✓ **Identify, Assess and Evaluate all the Risks** associated with your
    - API
    - Formulation
    - Process
  - ✓ **Utilize all the prior knowledge** and experience to identify and assess the high risks
  - ✓ **Plan and Design your Experiments** addressing all high risks attributes and parameters

**Now we are ready to build the control strategy in a systematic and efficient way**

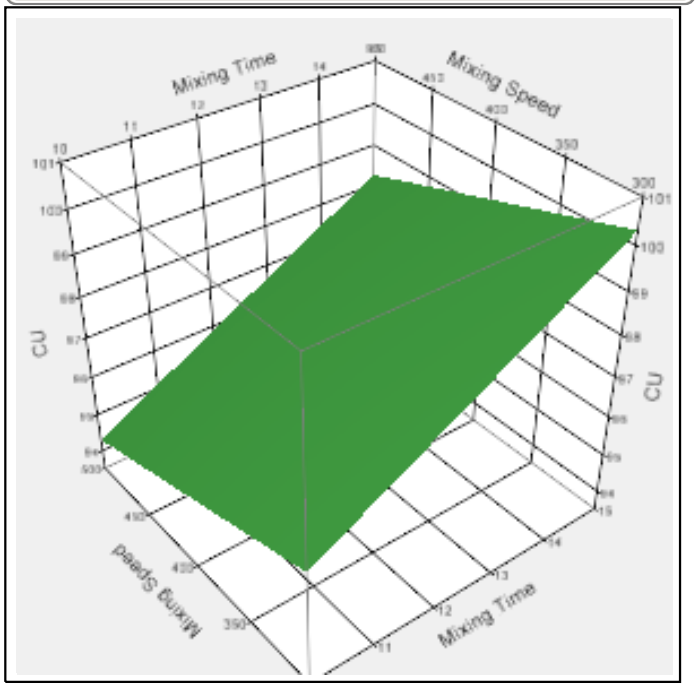
## Example of Initial Process Risk Assessment on Drug Product Attributes (IR Case Study)

| | Process | | | | | |
|---|---|---|---|---|---|---|
| **Drug Product CQA** | **Pharmacy / Dispensing** | **Blending** | **Roller Compaction** | **Milling** | **Final Lubrication** | **Compression** |
| **Assay** | High | Low | Low | Low | Low | High |
| **Impurity** | Low | Low | Low | Low | Low | Low |
| **CU** | Low | High | High | High | Low | High |
| **Dissolution** | Low | Low | High | High | High | High |

# Effective Risk Management: ‘only following the QbD way’

- CQA (CU) link to CMAs and CPPs via Design of Experiments and Multivariate Data Analysis:

**CU**




**Prediction Expression**

89.75
+0.78823529411765*Mixing Time
+-0.0102941176471*Mixing Speed
+2.35294117647058*Ribbon Density
+0.01470588235294*FB PSD-% Fines

## Example of Application of Control Strategy to Mitigate Identified Risks in Process Parameters (IR Case Study)

| | Process | | | | | |
|---|---|---|---|---|---|---|
| **Drug Product CQA** | **Pharmacy / Dispensing** | **Blending** | **Roller Compaction** | **Milling** | **Final Lubrication** | **Compression** |
| **Assay** | **Controlled by Weight** | **Low** | **Low** | **Low** | **Low** | **Controlled by tablet weight** |
| **Impurity** | **Low** | **Low** | **Low** | **Low** | **Low** | **Low** |
| **CU** | **Low** | **Controlled by mixing time and speed** | **Controlled by granule properties** | **Controlled by granule properties** | **Low** | **Controlled by tablet weight and appropriate feed settings** |
| **Dissolution** | **Low** | **Low** | **Controlled by ribbon density** | **Controlled by granule properties** | **Low** | **Controlled by tablet hardness** |

# Don’t forget to….

- Identify and capture critical information
- Transfer knowledge effectively to manufacturing plants
  - Product, process, methods, and other critical information
  - Handoff at successful completion of validation to assure timely launch
- Establish a clear process for problem resolution
  - QbD development will enable faster problem resolution by capturing all critical aspects of the development and their control strategy

# A cautionary note to keep in mind….

Thoughts from Grant Heinicke – from his May 2011 GPhA meeting presentation

- How will industry assess that QbD has worked?
  - Faster approval
  - Meaningful regulatory flexibility
  - Less regulatory question
- How will the FDA assess that QbD has worked?
  - Reduction in product failures
  - Reduction in product withdrawals
  - Reduction in customer complaints

# A cautionary note to keep in mind….

Thoughts from Grant Heinicke – from his May 2011 GPhA meeting presentation

**Focus on quality or curiosity…….**

- The endless "What if…?"
  - What if polymorph changes?
  - What if drug diffuses into a coat?
  - What if plasticizer evaporates?
  - What if the particle size were at the upper limit?
  - What if the viscosity was at the lower limit?
- We've seen applications with….therefore, it could always happen
- Counter balance with industry success

*It's neither the strongest of the species, nor the most intelligent, but the those that are most responsive to change that survive*

*- Charles Darwin*

*It is just the beginning….*

*A long way to go….*

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# Regulatory Assessment of Applications Containing QbD Elements - European Union (EU) Perspective

ACPS-CP meeting, 27 July 2011

**Evdokia Korakianiti, PhD**

Quality of Medicines Sector, Chemicals
European Medicines Agency

An agency of the European Union

# Presentation Overview

- About the Agency

EU perspective on:

- QbD and the patient
- Where we are
- What we have done so far
- What are the challenges
- What needs to be done further

# Science. Medicines. Health.

The mission of the European Medicines Agency is to foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health.

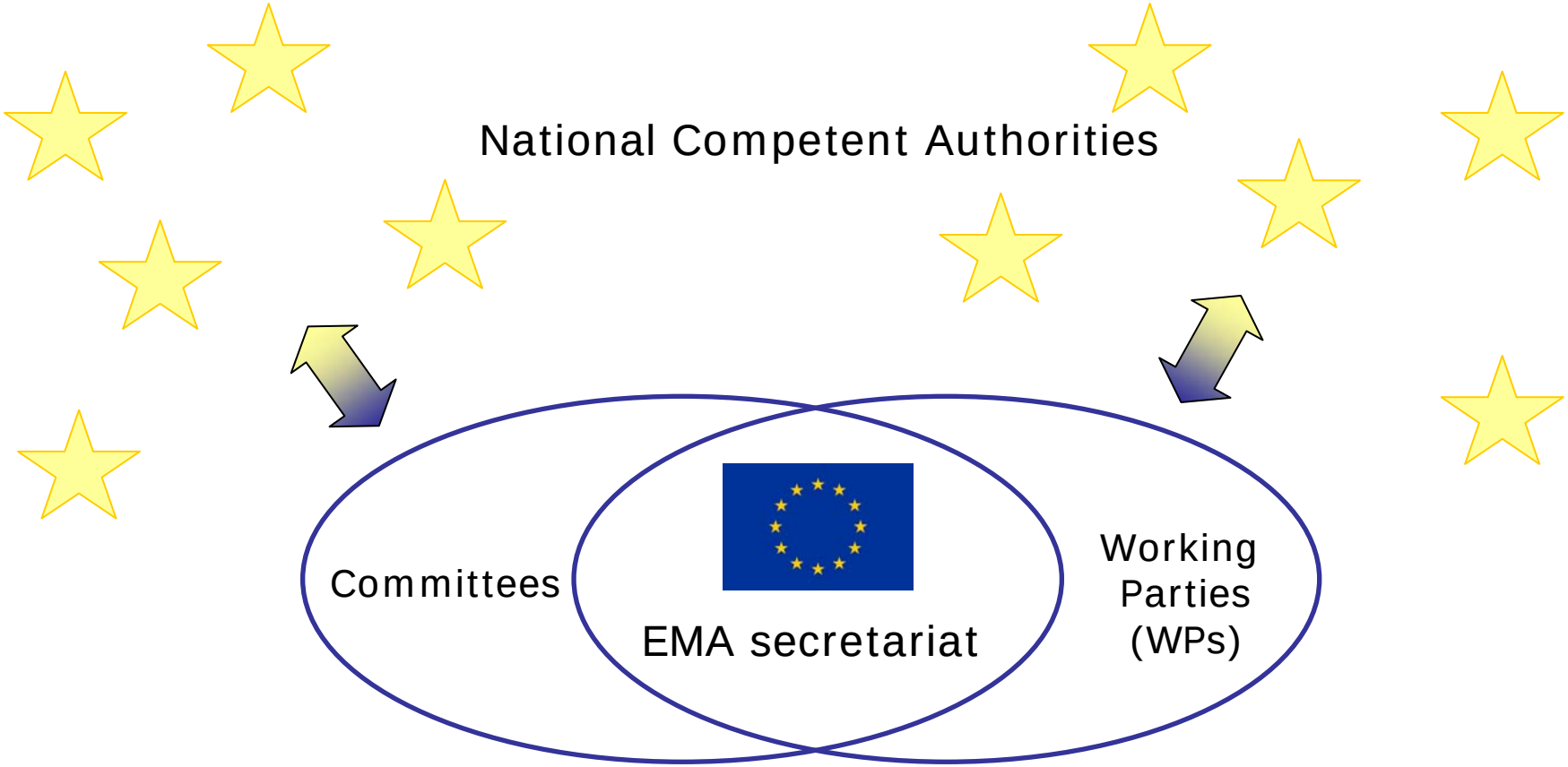
# Our partners in Europe

- **Single market** for certain pharmaceuticals
- **Same product information** to patients and healthcare professionals

- 500 million users of medicinal products
- 27 EU Member states
- > 45 national competent authorities
- > 4 900 European Experts
- EU institutions: European Commission, European Parliament, other EU agencies (EMCDDA, EFSA, ECDC, Translations Centre)
- EDQM (Council of Europe)

# European Regulatory Network

## 4,900 European experts



# EMA Scientific Committees

**CHMP**
(Committee for Human Medicinal Products) Chair: Dr E. Abadie

**CVMP**
(Committee for Veterinary Medicinal Products): Chair Dr A. Holm

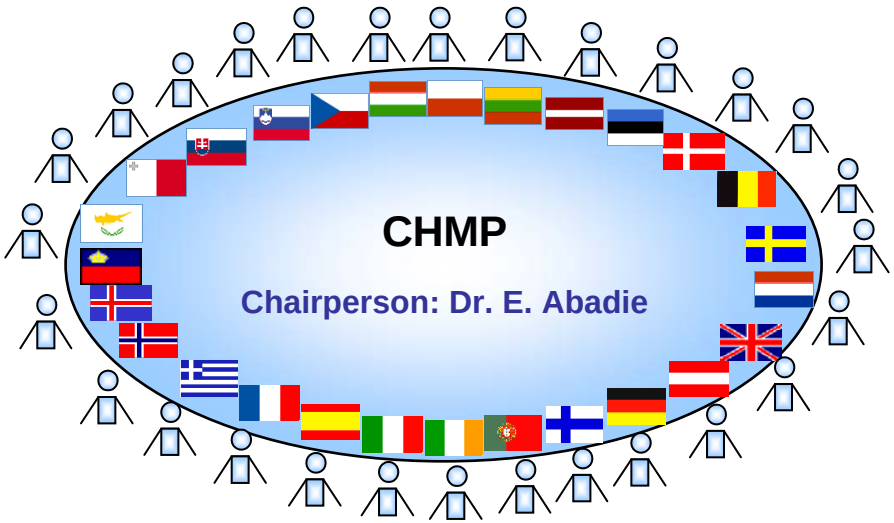
**HMPC**
(Committee for Herbal Medicinal Products) Chair: Dr W. Knoss

**COMP**
(Committee for Orphan Medicinal Products) Chair: Prof K. Westermark

**CAT**
(Committee for Advanced Therapy Medicinal Products) Chair: Dr Ch. Schneider

**PDCO**
(Paediatric Committee) Chair: Dr D. Brasseur

# Committee for Medicinal Products for Human Use



**max. 5 Co-opted CHMP members**

PhVig

Safety

Quality

+ Working parties

Biologics

Patients and Consumers

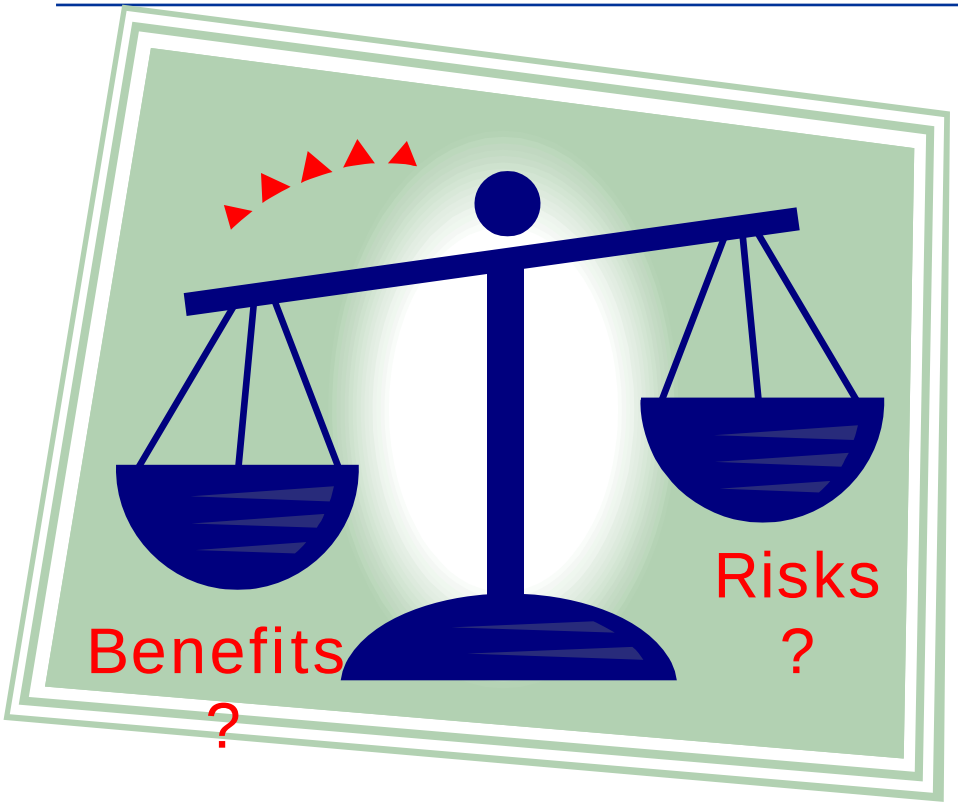
Scientific Advice

+ *Ad hoc* working parties

e.g. Biosimilar Medicinal Products Working Party

Or working groups e.g. EU PAT Team

# Quality by Design (QbD) and the patient




**QbD**:

"Build quality into the product"

= reducing uncertainties→

**Benefit to the patient**

- Systems approach
- Leverages information/ knowledge
- Smart study designs, tools
- Better decision-making (risk assessment and management)

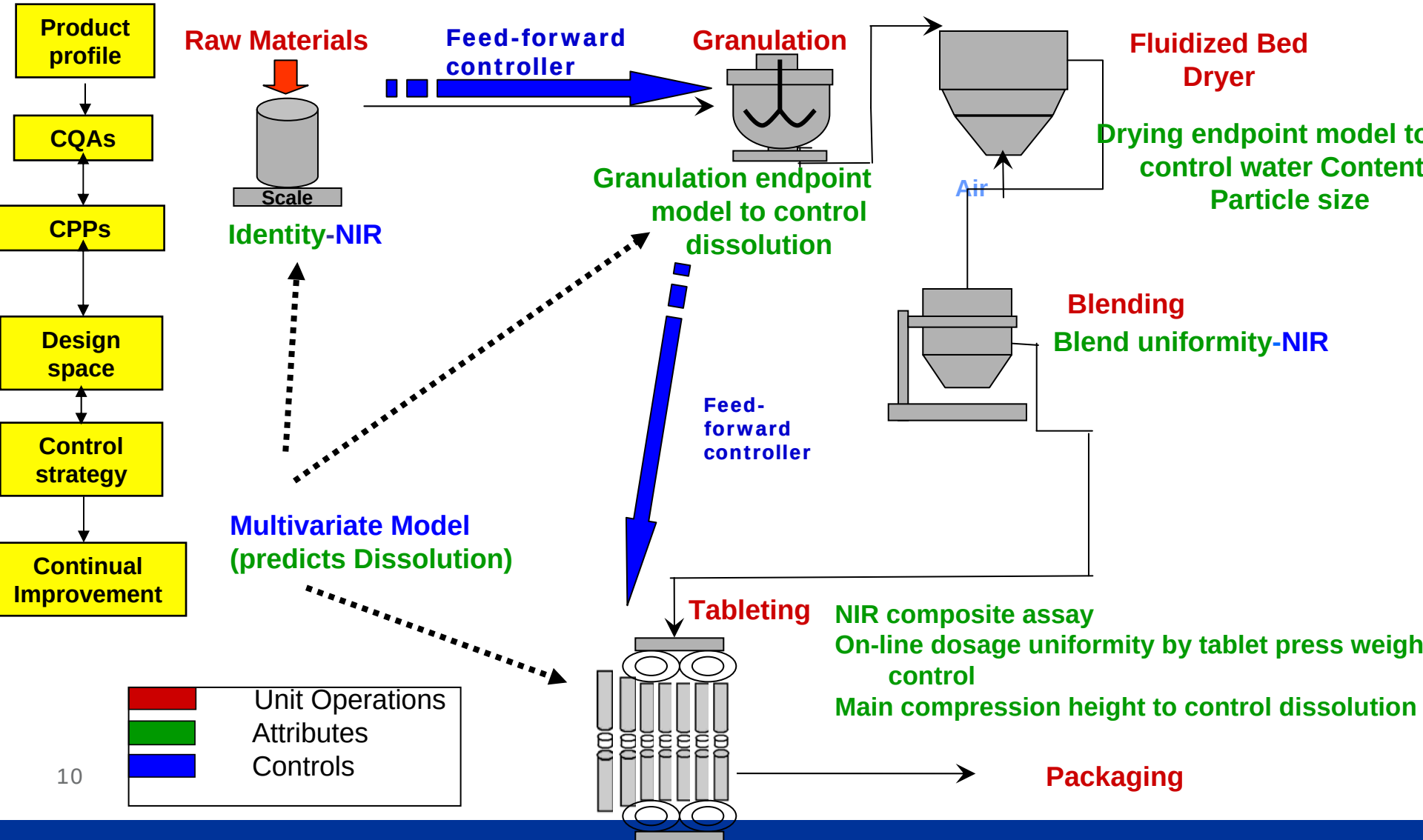
# What is different in a QbD dossier

Submissions with enhanced and sound development studies that lead to increased Product and Process understanding

Systematic use of the following tools:

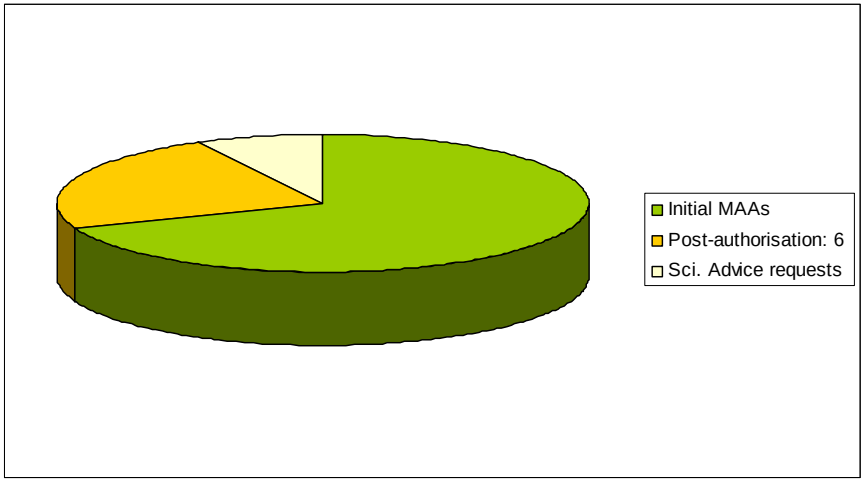
- Risk assessment
- Statistical tools
- Process Analytical Tools for monitoring the progress of the process “real time”
- Controls, for adjusting the process “real time”

# Example of a QbD application



# Where we are?
# QbD submissions in Centralised Procedure (CP)

- No of submissions received so far (NCEs)
  - Initial MAAs: 18 (4 incl. RTRT)
  - Post-authorisation: 6
  - Sci. Advice requests: 2




- Biologicals?

Initial MAAs: 2 (1 withdrawn on safety grounds), some at pre-submission level

- Generics?

None so far, BUT facilitating efficiency improvements provide opportunities for both sectors of the pharmaceutical industry

# Where we are? QbD submissions in CP

- The numbers of applications with QbD and / or PAT elements received are steadily increasing
- The content of the QbD submissions is now more comprehensive
- It seems that the companies that have received approval for QbD approach in one product are then implementing QbD across several of their products
- Applicants start exploring Real Time Release Testing and Continuous Process Verification (CPV)
- First contacts on continuous processes

# Where we are? ICH Regulatory toolbox

- ICH Q8, Q9 and Q10
- ICC- IWG Questions and Answers
  - Knowledge Management, Design Space, Real Time Release, Control Strategy and Pharmaceutical Quality System
- Points to consider on :
  - Criticality of Quality Attributes and Process Parameters
  - Control Strategy
  - Level of Documentation R/A and DoE

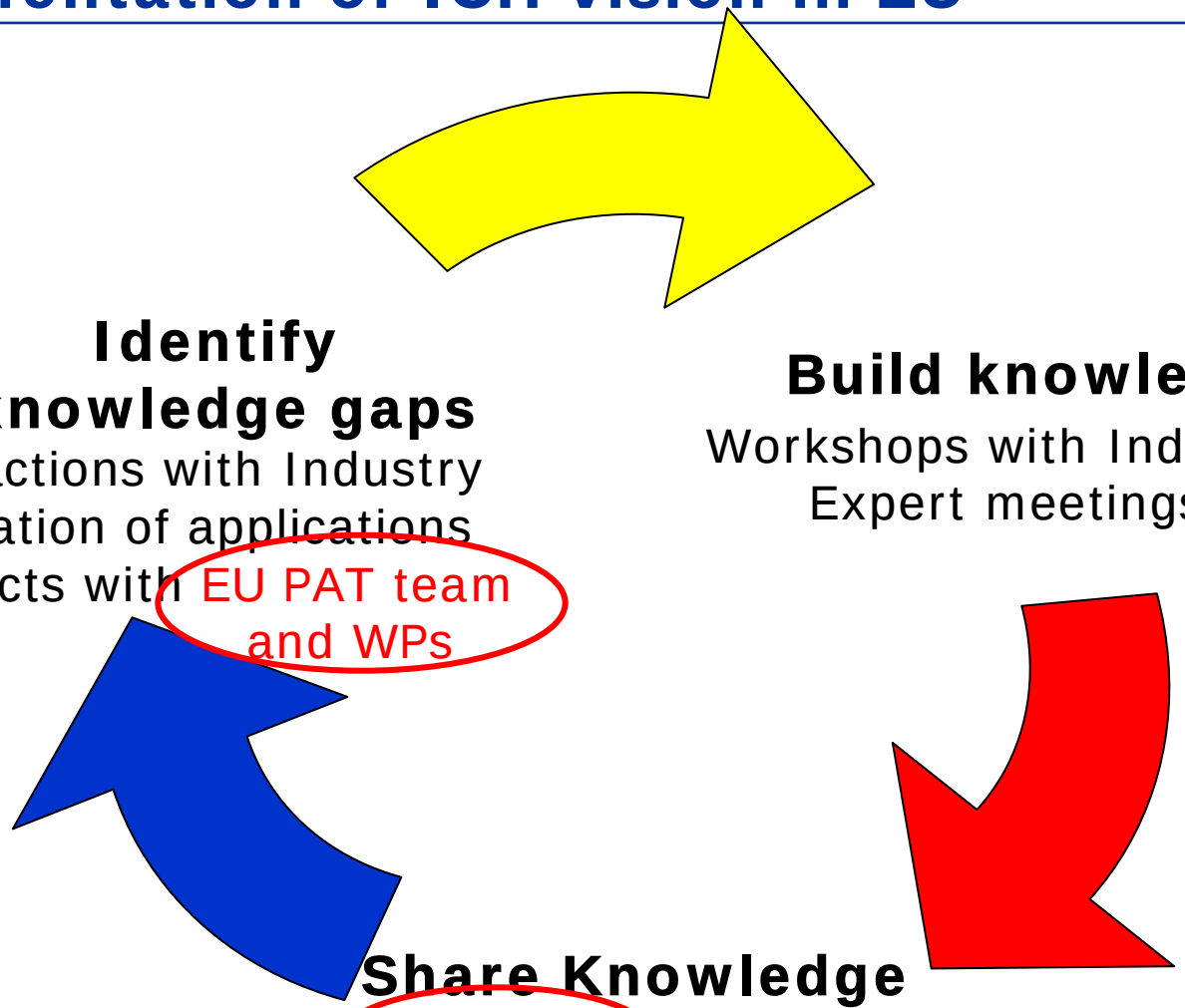
New topics

- Additional Points to consider to come:
  - Design space, modelling, process validation/continuous process verification



*http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html

# What have we done?
# Implementation of ICH vision in EU



# What have we done? EU PAT Team

**Aim:** Prepare a harmonised approach within EU on assessment and inspection of QbD submissions

**Activities:**

- Scientific discussions with applicants at pre- submission level
- Advice during evaluation upon request from Rapporteurs
- Training of assessors
  - 3 trainings for Assessors and Inspectors, ICH-WG training, regular presentations to Working parties
- Workshops with Industry
  - EMEA-EFPIA Workshops on Design Space (2006) and 'Quality by Design' (2009)
  - Mock Inspections /Mock submissions

# What have we done?
# Guidelines revision by Quality Working Party (QWP)

- Use of Near Infrared Spectroscopy (NIRS) by the Pharmaceutical Industry and the Data Requirements for New Submissions and Variations (EMEA/CHMP/CVMP/WP/17760/2009 Rev 1)* *(draft under public consultation)*

- Real Time release Testing (EMA/CHMP/QWP/811210/2009)* *(draft under public consultation)*

- Process validation (EMA/CHMP/CVMP/QWP/809114/2009)* *(concept paper released)*

*http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000081.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580027546

# What are the challenges?

- Common misconceptions
- Presentation of information in dossiers
- Clarification of regulatory requirements
  - At ICH-IWG and regional level
- Enable post-approval regulatory flexibility
- Harmonised implementation

# What are the challenges? Common misconceptions

- QbD = more scrutiny, more questions, delays in approvals
- QbD = pre-approval inspections, delays in approvals
- Design Space (DS) = DOEs
- Release based on compliance with DS (no need for specifications)
- Criticality vs risk: If a parameter is controlled it stops being critical (common misconception)

# What are the challenges? Presentation of information in dossiers

Summary of risk assessment (R/A) outputs (extract from an application file): what is often missing

| CQAs | Dry mix | Wet granulation | Wet mass de-lumping | Drying | Dry milling | Blending | Comp-ression | Coating | Packing |
|---|---|---|---|---|---|---|---|---|---|
| Assay | Low | Low | Low | Low | Low | Low | Low | Low | Low |
| Degradation products | Low | Low | Low | Low | Low | Low | Low | Low | Low |
| Uniformity of dosage unit | Low | Low | Low | Low | Low | Low | Low | Low | Low |
| Dissolution | Low | Medium | Low | Medium | Medium | Medium | Medium | Low | Low |
| Microbiology | Low | Medium | Medium | Medium | Low | Low | Low | Low | Low |
| **Non-CQAs** | | | | | | | | | |
| Appearance, eg, tablet picking | Low | High | Medium | Low | Medium | Medium | Medium | Low | Low |
| Hardness | Low | High | Medium | Low | Medium | Medium | Medium | Low | Low |
| Friability | Low | Medium | Medium | Low | Medium | Medium | Medium | Low | Low |

Key to risk assessment:
Low = Low risk of unit operation causing failure to achieve the quality attribute [a]
Medium = Medium risk of unit operation causing failure to achieve the quality attribute [a]
High = High risk of unit operation causing failure to achieve the quality attribute [a]
([a] = Risk was assessed considering probability, detectability and severity)

# Example of an acceptable R/A presentation

**Important!**

What is the **Impact** that ---------- will have on purity? 1) minimal 5) moderate 9) significant

What is the **Probability** that variations in ---------- will occur? 1) unlikely 5) moderately likely 9) highly likely

What is our **Ability to Detect** a meaningful variation in ---------- at a meaningful control point? 1) certain 5) moderate 9) unlikely

| Unit Operation | Parameter | IMPACT | PROB. | Detect | RPN | Comments |
|---|---|---|---|---|---|---|
| Distillative Solvent Switch | Temperature / Time, etc. | 1 | 5 | 1 | 5 | Distillation performed under vacuum, at low temperature, minimizing risk of hydrolysis |
| Distillative Solvent Switch / Crystallization | Water content at end of Distillation (Crystallization Feed) | 9 | 5 | 1 | 45 | Higher water = higher degradation<br>In process control assay should ensure detection and |
| Crystallization -- API Feed Solution | Feed Temperature | 9 | 5 | 1 | 45 | Higher temperature = higher degradation<br>Temperature alarms should enable quick detection and control |
| Crystallization -- API Feed Solution | Addition Time | 9 | 1 | 5 | 45 | Longer time = higher degradation<br>Detection of prolonged addition time may occur too late to prevent some degradation |
| Crystallization | Seed wt percentage | 1 | 1 | 1 | 1 | This parameters cannot impact impurity rejection, since no rejection of hydrolysis degradate occurs. |
| Crystallization | Antisolvent percentage (charge ratio) | 1 | 1 | 1 | 1 | This parameters cannot impact impurity rejection, since no rejection of hydrolysis degradate occurs. |
| Crystallization | Crystallization temperature | 1 | 5 | 1 | 5 | Temperature is low enough that no degradation will occur. |
| Crystallization | Other crystallization parameters | 1 | 1 | 1 | 1 | These parameters cannot impact impurity rejection, since no rejection of hydrolysis degradate occurs. |



Example from ICH-IWG Case Study: Risk Assessment (FMEA): Purity Control

# What are the challenges? Presentation of information in dossiers

- Current approach: The less that is included the better, nice graphs are enough…
- Often only conclusions of studies are presented with no explanation about how they have been reached
- DS boundaries not clearly described (which parameters consist the DS and their ranges)
- Ranges investigated in lab scale not corresponding with the DS boundaries with no further explanations
- No information on statistical validity of models / DoEs
- QbD dossiers need to be better structured, the aim of the studies should be clear

# What are the challenges? Clarification of regulatory requirements

## Design space (DS)

- DS limits vs statistical risk
- DS verification vs scale and equipment
- Movement to less well verified areas within a DS
- DS for individual unit operations, what is the interaction amongst all the unit operations in the manufacturing process?

## Modelling

- When is a model appropriate for RTRT and CPV?
- How will model validity be verified through the product lifecycle?
- Model vs risk to quality

## Manufacturing process descriptions

vs post approval changes

## Quality systems and QbD

What change constitutes a variation and what an update that can be handled under the Quality System of the company?

## QbD and established regulatory standards

e.g. Acceptance criteria for content Uniformity when using large sample sizes (ongoing work from EDQM)

# What are the challenges? Post-approval changes

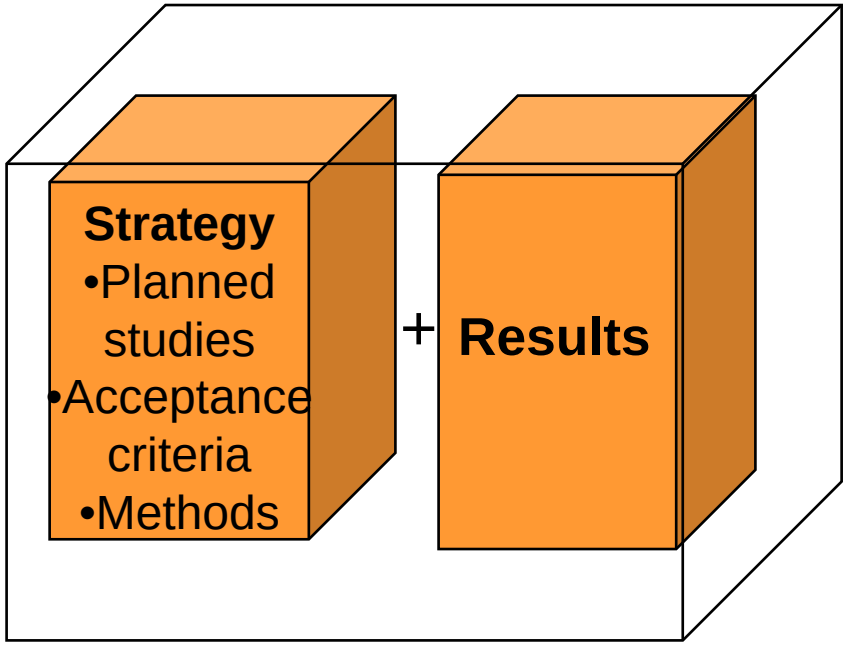
One size fits all!

From J. Berridge, *PQRI March 2005*

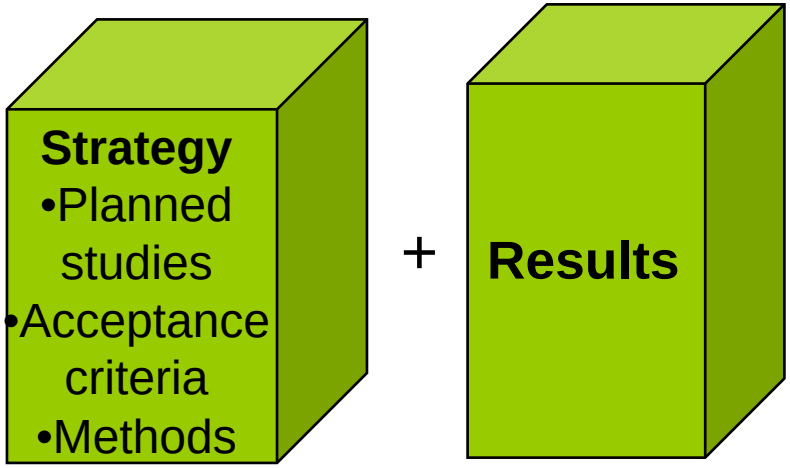
- Should better understanding of process risks mean less regulatory commitments and how?
- Risk based framework that enables handling of changes post approval
- **Risk based protocols**
  - Draft Q&A on EMA website*

*http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000478.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580251bd9

# Post-approval Change Management Protocols




**Currently Evaluation of a proposed variation as a 'whole' (Strategy + Results)**




**Early Step 1:**

**Submission of a Protocol**

Major Variation (Type II) or in initial MAA

**Quick Step 2:**

**Implementation of the change**

Minor Variation (Type IAIN or IB)

# What are the challenges? Harmonised implementation in EU

- Assessment scrutiny ⟷ **Risk to finished product quality**

- Adequate expertise at a time of limited resources at national and European level.

- Harmonisation
  - Training, Guidance, Peer review

- Assessor/Inspector interaction
  - -Borderline between assessment and inspection
  - -Inspectors focus on system related issues
  - -Joint inspections

# What are the challenges? Harmonised implementation in ICH regions

EMA-FDA pilot for parallel assessment of QbD applications
(NCE products only)

**Objective :**
Increase assessors awareness **using actual applications** and to ensure consistent implementation in the evaluation process of ICH Q8-10 concepts between EU and US

**Outcome**
- **Same LoQ and LoOI** for the parts of the application subject to the pilot
- Guidance development

For more details:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/document_listing/document_listing_000228.jsp&murl=menus/partners_and_networks/partners_and_networks.jsp&mid=WC0b01ac058003176e

# What needs to be done

- Guidance to address the current challenges and future trends
  - Multivariate Statistical Process Control (MSPC) based models proposed as surrogate for traditional release tests
  - Defining clinically relevant design space
  - Setting clinically meaningful specifications
  - QbD and analytical development
  - Implementation of the QbD paradigm for continuous manufacturing

- Share knowledge with the network of Assessors and Inspectors in EU (Training, Guidance)

- Harmonised implementation across ICH regions

# Summary

- Issues keep arising as we gather experience
- Assessors are requested to evaluate new types of data – Need for appropriate expertise
- Guidance documents are being drafted/revised
- Need to continue dialogue with Industry
- EU is actively participating in the ICH Implementation Working Group activities to ensure a harmonised approach in the implementation

# Final remark

QbD->Better process and product understanding

↓

Higher assurance of product quality and better management of risks

↓

Benefit to the patient

# Thank you for your attention!

# Questions?

**Acknowledgements:**

EU PAT Team: J-L Robert, K.Pugh, L.Ertle, M.Diller, R.Cejka, K.Ho, M.Welin, M.Wierer, M.Hiob, M.Catibusic, G.Lorenti, D.Makohon

# Regulatory Assessment of Applications Containing QbD Elements - FDA Perspective

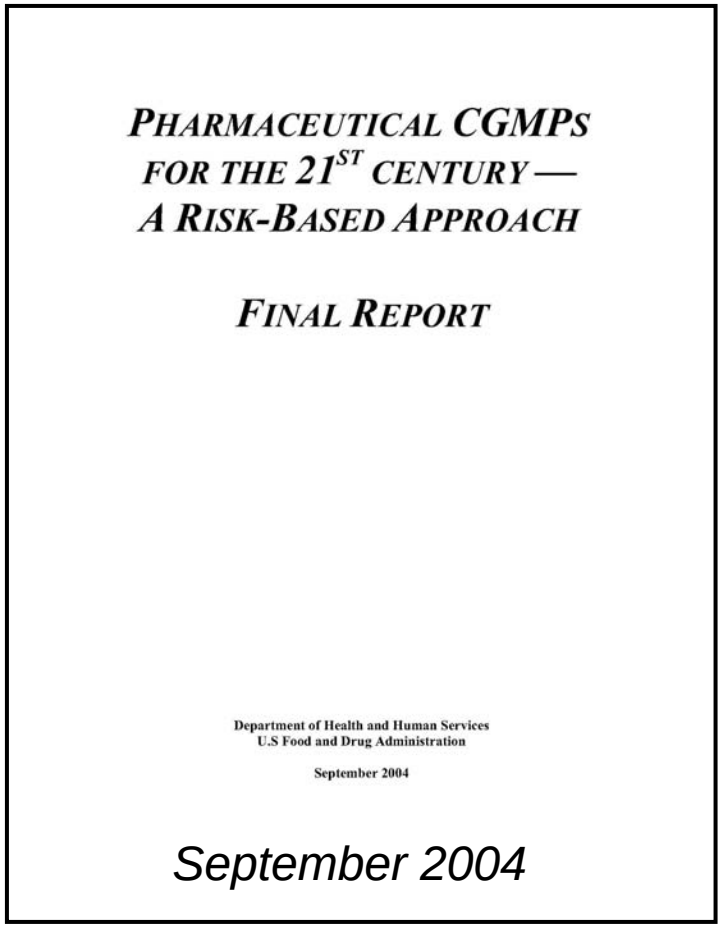
*Meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology*
*July 27, 2011*
*Silver Spring, MD*

**Sarah Pope Miksinski, Ph.D.**
**Branch Chief, Branch 2/DNDQA1**
**Office of New Drug Quality Assessment**
**OPS/FDA/CDER**

# Outline

- QbD submission update for new drugs
- Review of QbD-based submissions
  - Guidances and MaPPs
  - Training efforts
  - Team based review process, Good Review Management Practices (GRMPs)
  - Reviewer participation in inspections
- Generic and biotechnology products
  - Office of Biotechnology Products (OBP)
  - Office of Generic Drugs (OGD)
- Conclusions

# FDA 21st Century Initiative (2004)


PHARMACEUTICAL CGMPS
FOR THE 21ST CENTURY —
A RISK-BASED APPROACH

FINAL REPORT

Department of Health and Human Services
U.S Food and Drug Administration

September 2004

September 2004

**Objectives:**

♦ Encourage the early adoption of new technological advances by the pharmaceutical industry

♦ Facilitate industry application of modern quality management techniques, including implementation of quality systems approaches

♦ Encourage implementation of risk-based approaches

♦ Ensure that regulatory review, compliance, and inspection policies are based on state-of-the-art pharmaceutical science

♦ Enhance the consistency and coordination of FDA's drug quality regulatory programs

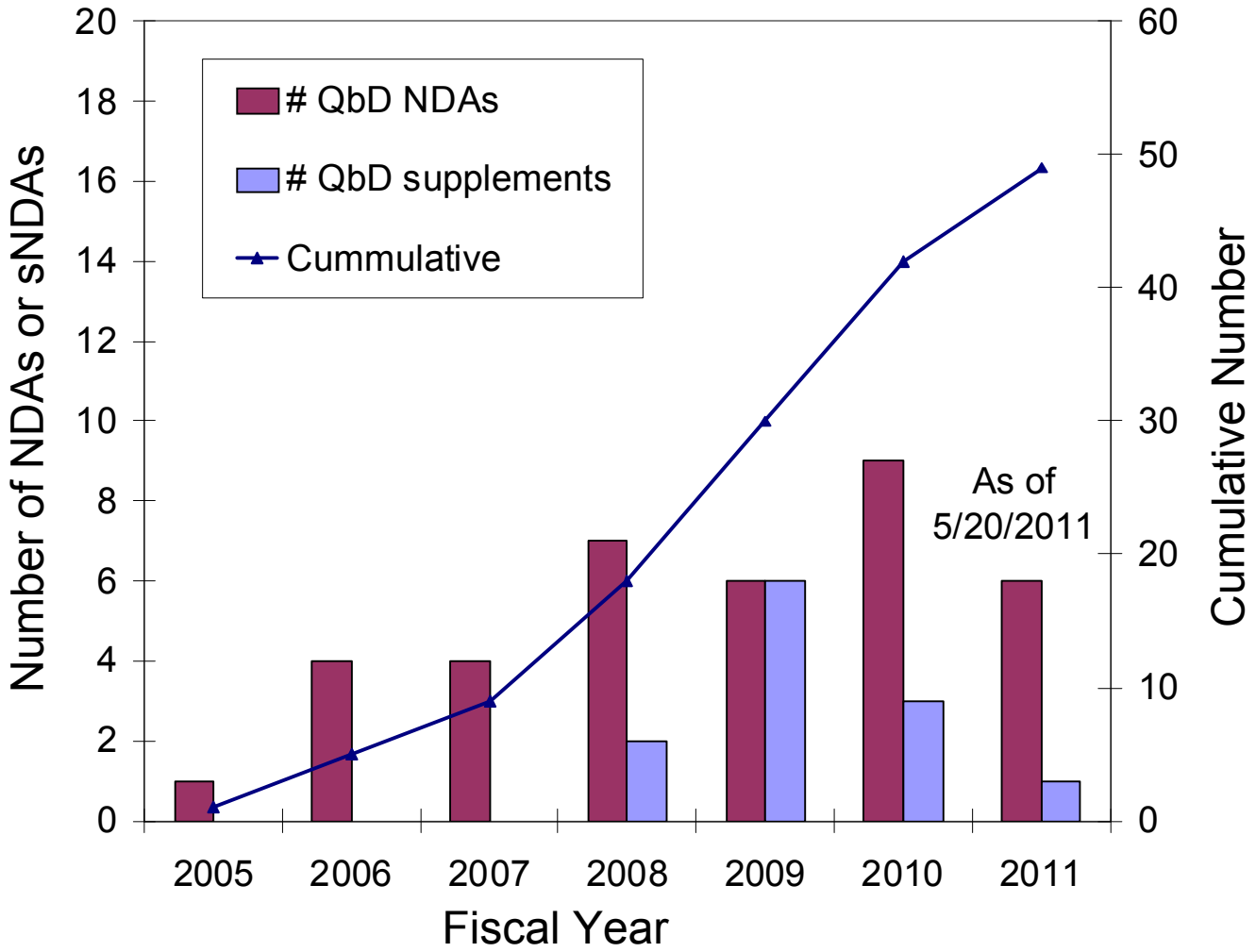
# ONDQA's CMC Pilot Program

- Initiated in July 2005
- Objectives
  - To provide participating firms an opportunity to submit/share QbD elements in CMC sections of regulatory submissions
  - To enable FDA to implement new QbD concepts
- Status Complete
  - 9 original and 2(3) supplemental NDAs accepted
  - 11 approved, 1 withdrawn (for non-CMC reasons)
- Provided valuable experience for industry and FDA in implementing QbD
  - Elements of QbD in submissions
  - Risk-based regulatory decisions were enabled
- Learning has been incorporated into ICH Q8R2

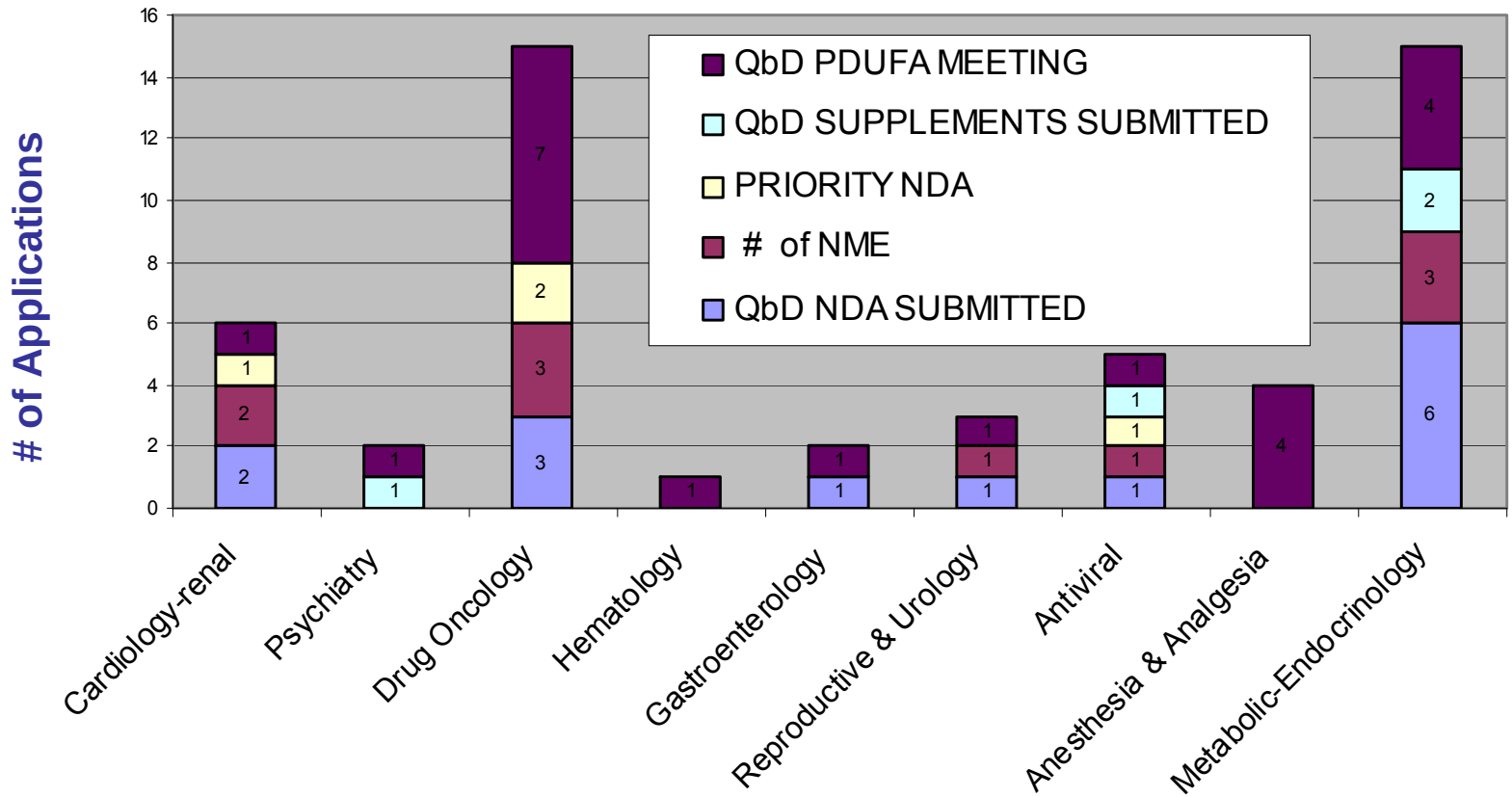
# Where we are…

- The number of QbD containing applications of new drugs has been increasing over the past 6 years
- QbD approaches (e.g., defining CQAs, developing design space) have been fairly well fleshed out by applicants and reviewers
- More experience is still needed for more advanced concepts (e.g., RTRT)
- QbD concepts are often utilized across many applications
  - Applications include more development information

# New Drug QbD Submissions



# QbD-Containing Applications (FY2010-11)






Clinical Division

# Where we want to be in ONDQA (1)

Develop and implement policy and procedures for reviewing QbD applications:

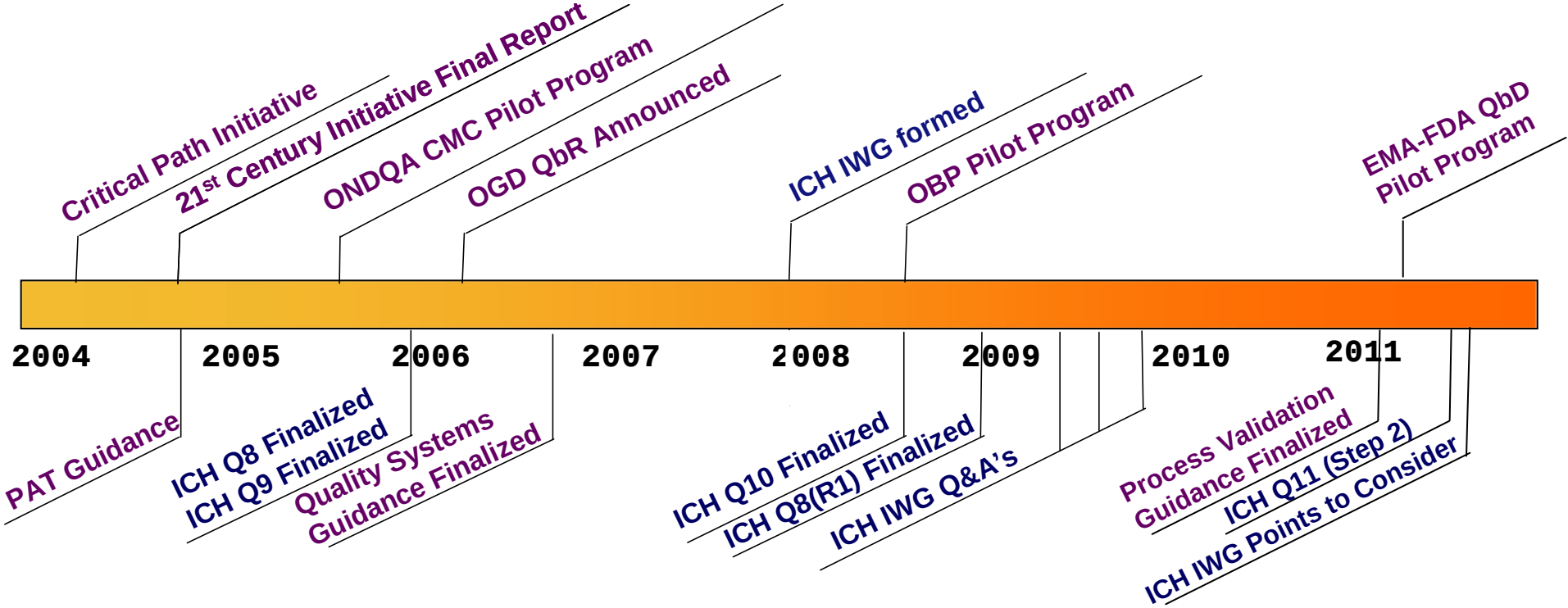
- Documented approaches for how to review QbD elements in applications
  - MaPPs and Guidance
- All ONDQA reviewers trained in review of QbD applications
  - Risk assessment, design space, etc.
- Develop a cadre of experts for some advanced concepts
- Institute and maintain systems for knowledge retention and capturing precedence

# Where we want to be in ONDQA (2)

- ONDQA envisions a continuing increase in the utilization of QbD elements in regulatory submissions
- ONDQA envisions a broader utilization of QbD elements for all applications

***Question: How can we facilitate this?***

# Quality-Related Guidance and Initiatives



# QbD Reviews – Guidances and MaPPs

- FDA Guidance in progress
  - Comparability Protocols (Revised Draft)
  - MDI/DPI (Revised Draft)
  - Residual Drugs in Transdermals (Final)
- ICH IWG Points to Consider
  - Complete – Criticality, Control Strategy, Level of Detail in Submission
  - Future plans - Process Validation, Role of Modeling, Design Space
- MaPPs – recently published and in progress
  - Applying ICH Q8-10 Principles to CMC Review
  - Review of Analytical Procedures using NIR Spectroscopy

# Reviewer Training in QbD Approaches

- Internal
  - Technical courses (e.g., design of experiments, statistics, chemometrics)
  - Internal regulatory discussions (e.g., Regulatory Briefings, QbD discussion group)
  - Invited speakers
  - Specific mentoring/team reviews
- External
  - Academic collaborations
  - Hands-on analytical and unit operations
  - Conference attendance/participation

# QbD Reviews – Team-Based Process

- Most QbD containing submissions are team-based reviews
  - ONDQA review team
    - Primary reviewers – Both CMC and Biopharmaceutics
    - ONDQA Project Manager
    - Supervisors (Branch Chief, Division Director)
    - Additional technical experts – Statistician, Microbiologist (as needed)
- Expanded review and inspection team
  - Office of Compliance – Compliance Officer
  - Office of Regulatory Affairs - Investigator

# QbD Review Process

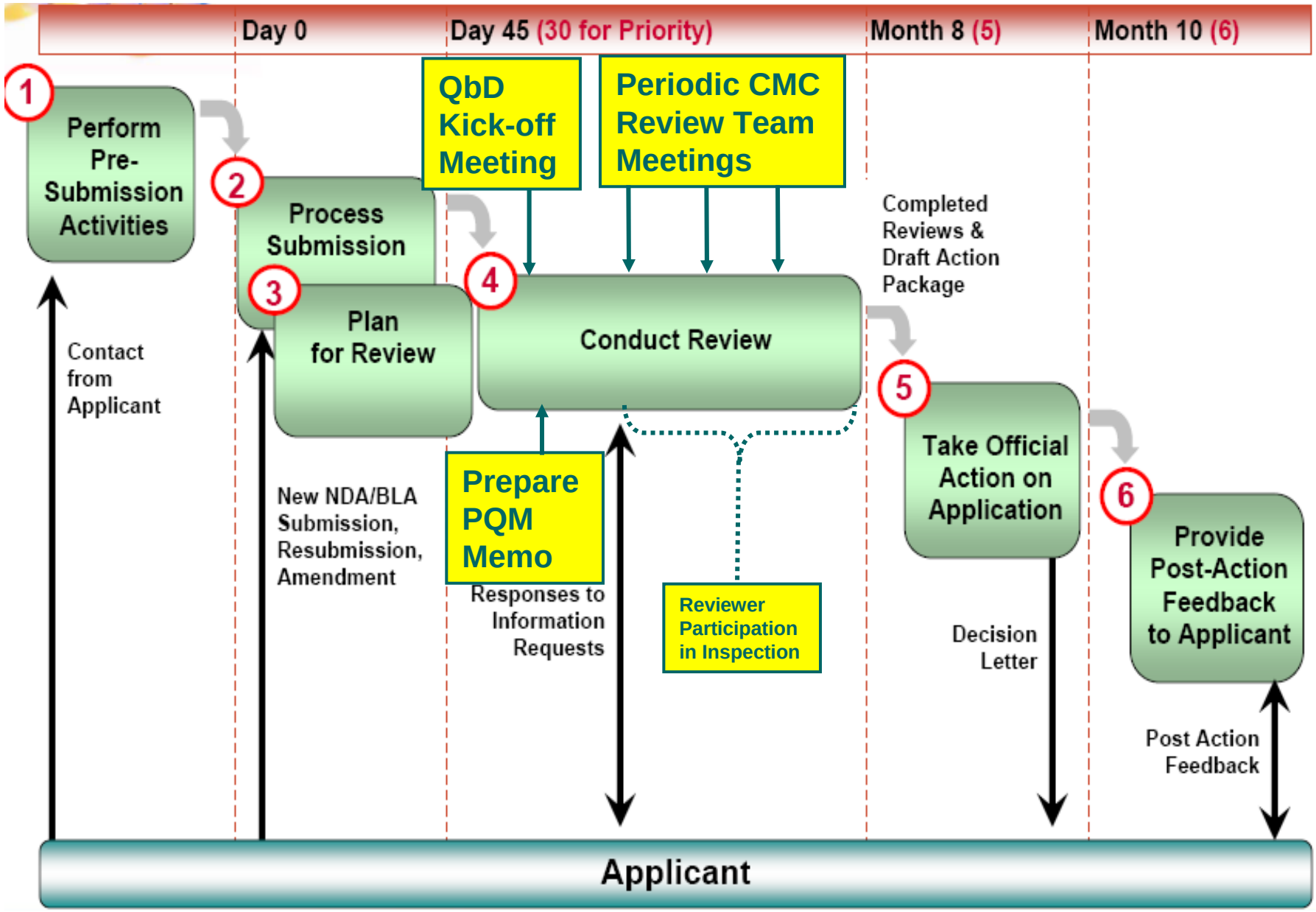
- QbD kick-off meeting
  - Invite review team, ONDQA experts, representatives from OC, ORA
  - Discuss potential product and process risks and review precedence
  - Discuss review deliverables and anticipated timing
- Product Quality and Manufacturing (PQM) Memo
  - Formerly the CFI Memo
  - Communicated to OC and ORA
- Periodic team meetings
- Team-developed information request (shortly following mid-cycle)
  - Help ensure consistency within office
- Review response
- Conduct inspections
  - Reviewer input and more frequent participation
- Finalize review

*Within 10-month GRMP dates for standard (6 months for priority)*

# Product Quality and Manufacturing Memo

- ONDQA-prepared memo to aid in communicating application-related information to OC and ORA
- Prepared relatively early in the review cycle to help with inspectional planning
- Contents include: product description, process summary, critical steps and controls, summary of product and process-related risks
- Currently prepared for:
  - Complex products and/or processes
  - Complex regulatory approaches (e.g., RTRT)
  - Applications with questionable manufacturing capabilities or suspect data integrity issues

# GRMPs - Timelines



# Reviewers on Inspection

- Reviewers have always had an opportunity to participate in inspections
- Traditionally, few NDA PAIs have reviewer participation
  - Certain review groups in FDA have a higher frequency of reviewer participation (OBP, CBER)
- In ONDQA, the frequency of reviewers participating in inspections has recently increased
  - More complex regulatory approaches (QbD)
  - Increased emphasis on shared knowledge and expertise

# Recent ONDQA Inspection Participation Activity

| Fiscal Year | # Reviewer Inspectional Trips |
|---|---|
| 2007 | 5 |
| 2008 | 4 |
| 2009 | 8 |
| 2010 | 16 |

***Includes PAIs for NDAs, PAIs for sNDAs, Pre-Operational Reviews and For-Cause Inspections***

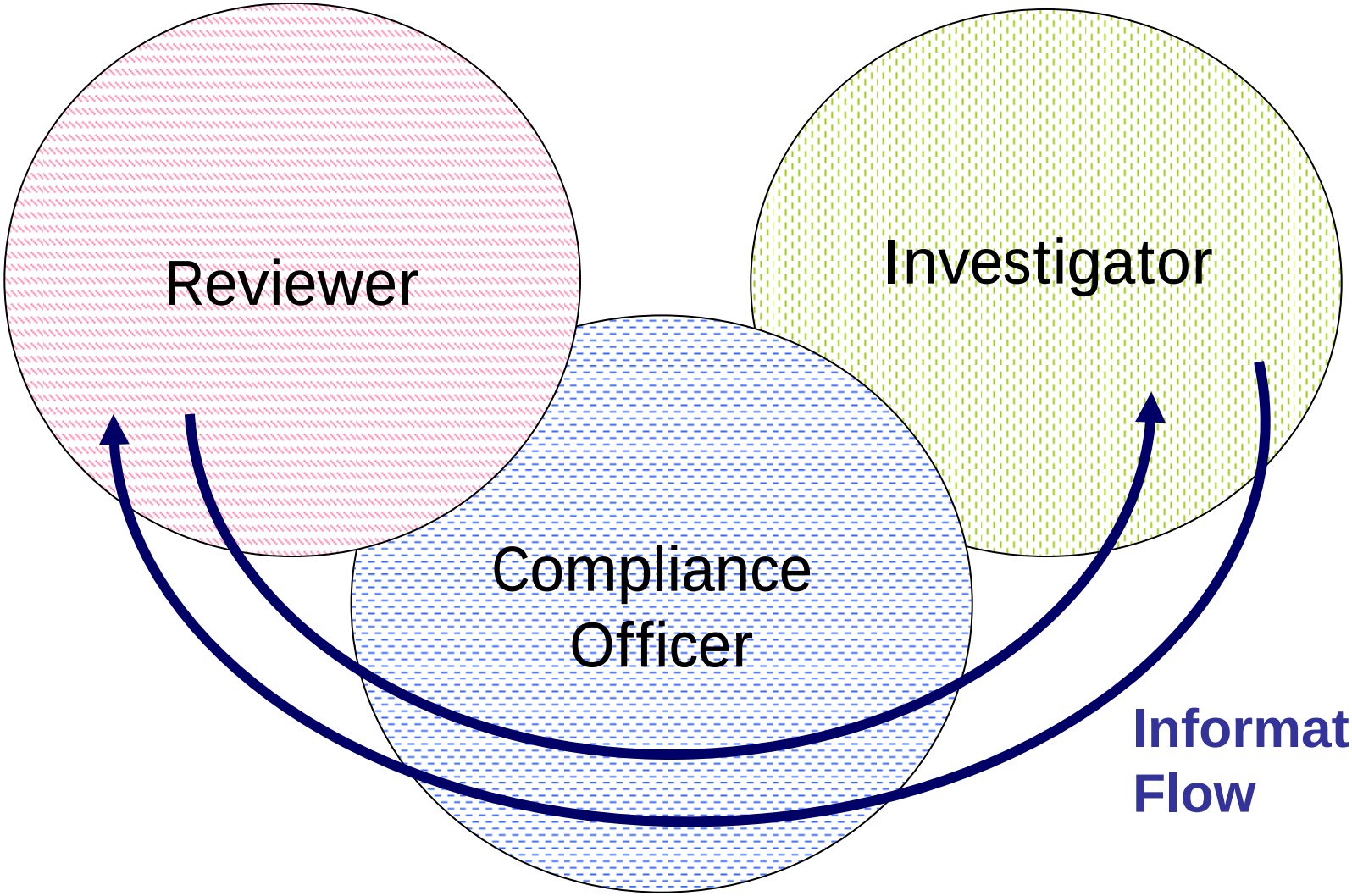
# Reviewer on Inspection: Value Added

- Value to Reviewer
  - Increased understanding of the process and product
  - Help resolve certain review issues related to application
  - Understand scale-up and process control rationale
  - Understand implementation of on-line monitoring systems and related models

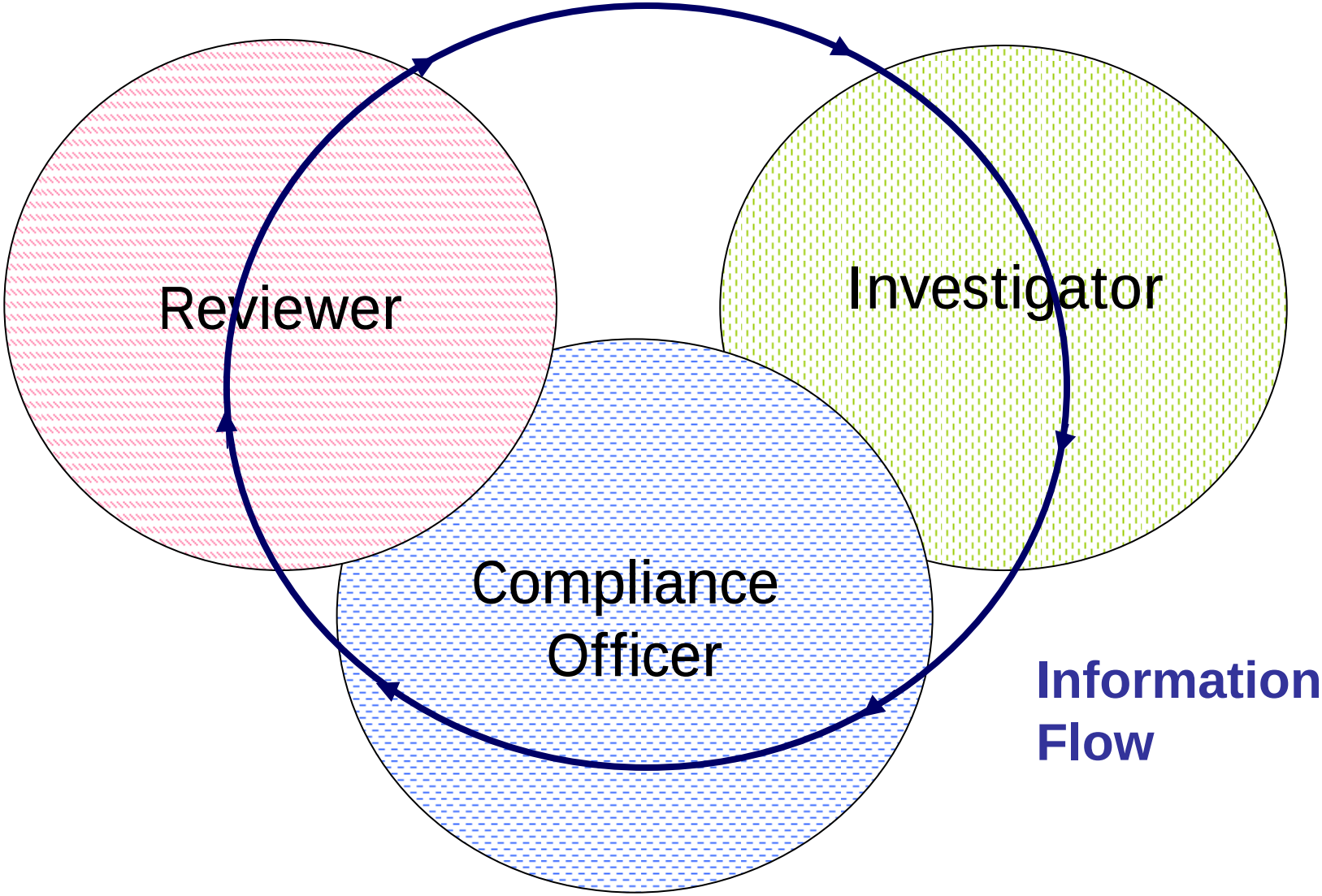
# Reviewer on Inspection: Value Added

- Value to Team
  - Reviewer provides specific areas of expertise and intimate knowledge of application
  - In-depth discussion and exchange of ideas based on expertise
  - More productive inspection
  - Superior understanding of product quality assurance for inspection team
  - Increased understanding and appreciation of other divisions' roles and responsibilities

# Traditional Model



# Integrated Approach



# QbD for Biotechnology Products

- QbD concepts apply to complex products; implementation may differ
  - Definition of CQAs may be complicated by product complexity and heterogeneity
  - Linking a large number of quality attributes to complex manufacturing processes is challenging
- OBP Pilot Program (*FR Notice July 2, 2008)*
  - To define clinically relevant attributes for protein products and link them to manufacturing processes
  - To consider QbD approaches to unit operations in supplements as well as original applications
  - To explore the use of protocols submitted under -(21 CFR 314.70(e) and 601.12(e)) for QbD submissions

# OBP QbD Biotech Pilot (1)

- The pilot was closed to new participants on 9/30/2010
  - 6 original applications (5 MAbs, 1 fusion protein)
  - 4 manuf. suppl. (2 MAbs, 1 Ther. Protein, 1 Multi-product)
- Multiple meetings have been held with many of the participants to discuss their QbD strategies
  - 4 in FY 2009
  - 9 in FY 2010
  - 5 in FY 2011 to date

# OBP QbD Biotech Pilot (2)

- One QbD manufacturing supplement with an expanded change protocol covering multiple products and manufacturing sites has been approved.
  - Evaluation of this supplement involved effective interactions between review and compliance functions at CDER.
    - MAPP 4730.3 OBP & DMPQ Interactions on BLAs
- Have seen risk assessments and DOE in some applications outside of the pilot program

# Biotech QbD Implementation

- Link to small-molecule learnings
  - ONDQA pilot and application experience
- ICH IWG, Q8R, Q9, Q10, Q11
- Staff participation in conferences, forums and training on QbD
  - Design of Experiments Training
  - Risk Management Workshop
- Mock case studies
  - A-Mab
  - EFPIA mock S2 to be published

# QbD for Generic Products (OGD)

- Meetings with the Generic Industry/GPhA
  - 3 QbD Workshops – June 2009, May 2010, May 2011
  - 4 QbD Roundtable Discussions – Jun 2009, Oct 2009, Feb 2011, Apr 2011
- QbD presentations at GPhA, AIChE, AAPS, DIA, NIPTE, FIP annual professional meetings
- 15+ peer reviewed publications on QbD concepts for generic drugs
- Industry feedback has focused on the use of prior knowledge and risk analysis

# OGD QbD Examples

- Intended to illustrate the types of development studies ANDA applicants may use as they implement QbD
- Provide a concrete illustration of the QbD principles from ICH Q8(R2)
  - Both IR and MR illustrate QbD principles
- Development of a real product may differ from the examples
- Number of experiments may depend on the experience of the applicant
  - This should be explained in the submission

Draft examples available online: http://www.gphaonline.org/events/past

# Generics - QbD Implementation

- All ANDAs are being submitted in Question-based Review (QbR) format
  - Already receiving applications containing QbD elements
- OGD has developed IR and MR QbD examples. To be finalized shortly
- OGD will begin comprehensive internal training on QbD in the Fall, 2011
- Further discussion with industry is expected through 2011 and 2012
- QbD to be fully implemented by January 2013

# Conclusions

- Implementation of QbD is progressing well
  - Steady increase in interest and applications
- Team-based approaches successfully utilized
  - Approaches are being extended beyond QbD applications
- Continued integration and communication is needed
- OPS envisions a broader utilization of QbD elements for all applications

# *Monograph Modernization Program*
## *Topic Introduction:*
## *FDA Monograph Modernization Task Group*

*Advisory Committee for Pharmaceutical Science*
*and*
*Clinical Pharmacology*
*July 27, 2011*

Co-chairs:

Paul R. Seo
CDER Office of Pharmaceutical Science

Larry A. Ouderkirk
CDER Office of Compliance

# Topics

- Topic Presentations - Overview
- Monograph Modernization - Introduction
  - Introduction/History
  - Past Examples: FDA-USP Modernization
- FDA Monograph Modernization Task Group (MMTG)
  - Origins
  - Task Group Charter
    - Composition
    - Purpose/Charge
  - MMTG Accomplishments and Future Objectives

# Topic Presentations

1. **Introduction and FDA Monograph Modernization Task Group (MMTG) Overview**
   Larry Ouderkirk - Office of Compliance (OC), CDER, FDA
2. **OTC Monographs: Improving Quality Assessment Standards**
   Reynold Tan, Ph.D. - Office of Drug Evaluation IV, Office of New Drugs (OND), CDER, FDA
3. **USP Perspectives**
   a. **USP Monograph Modernization Initiative – Small Molecules**
   Karen Russo, Ph.D. - Vice President, Small Molecules, United States Pharmacopeia (USP)
   b. **USP Monograph Modernization Initiative - Excipients**
   Catherine Sheehan, M.S.- Director, Excipients, USP
4. **Industry Perspective**
   a. **USP Monograph Modernization – The OTC Industry Initiatives**
   Rachael Roehrig, Ph.D. - Director, Technical & Scientific Affairs, Consumer Healthcare Products Association (CHPA)
5. **FDA/USP Science Collaboration**
   Jon Clark, M.S. – Associate Director for Program Policy, OPS/CDER/FDA

# Monograph Modernization - Introduction

- USP monographs for active drug substances/drug products and NF monographs for inactive pharmaceutical ingredients (excipients) are recognized in the FD&C Act as official standards of strength, quality, and purity.
- USP-NF standards are continually revised; however, with the evolution of a global drug supply, compendial drug requirements have become increasingly important to FDA as an enforcement tool.
- For many years, FDA/CDER has actively assisted USP in revising USP and NF.
- USP has recently increased its efforts to modernize USP/NF monographs, with FDA assistance.

# Why a Need for Monograph Modernization - History

- FDA's concerns with outdated monographs include:
  - Inadequate test methods, especially for *Identification* (ID), can render articles more vulnerable to contamination or adulteration (including economically-motivated adulteration).
  - Inadequate or missing tests or limits for impurities can increase risk to public.
  - USP monographs for OTC drugs are especially important because, unlike NDA/ANDA drugs, most do not undergo pre-approval review before marketing.
  - NF monograph tests for excipients are also important, especially since certain excipients are used in many drug products, often at high proportion of composition.

# Monograph Modernization - Examples

Examples of FDA-USP Modernization Efforts:

- USP Glycerin Monograph
  - **May 2007**: FDA issued a guidance on *Testing of Glycerin for Diethylene Glycol* (DEG) that referenced USP Glycerin monograph tests
  - **April 2007**: FDA requested USP to place tests/limits for DEG into monograph's *Identification* test
  - **May 2009**: USP monograph with revised *Identification* tests/limits for DEG/EG (ethylene glycol)

# Monograph Modernization – Examples (continued)

USP monographs for similar articles were also revised to include DEG/EG tests/limits in ID test:

- February 2010:
  - Propylene Glycol
  - Sorbitol Solution
  - Sorbitol-Sorbitan Solution
  - Noncrystallizing Sorbitol Solution
- August 2010:
  - Maltitol Solution

# Monograph Modernization – Examples (continued)

USP Heparin Sodium Monographs

- **March 2008:** Heparin, an anticoagulant, was adulterated (2% - 60%) with oversulfated chondroitin sulfate (OSCS). USP methods did not detect OSCS. At least 81 US deaths were reported.
  - Two test methods were developed by FDA/USP/academia/industry to detect OSCS:
    - Proton NMR - $^{1}$H NMR
    - Capillary Electrophoresis (CE)
- **June 2008:** USP *Revision Bulletin* posted to website incorporated $^{1}$H NMR and CE test methods into *Identity* test to detect the OSCS adulterant (USP Stage 1 revisions)
- **October 2009:** USP incorporated Stage 2 revisions to further strengthen the monograph tests

# Monograph Modernization – Phase II

## USP Convention - April 2010

- FDA supports USP 2010-2015 Resolutions to:
  - Strengthen USP's focus on core compendial activities to ensure relevant, timely, accurate public standards
  - Strengthen the USP-FDA relationship…to better provide and maintain up-to-date national standards for legally marketed drugs….
    - Modernizing USP-NF Monographs, to:
      - Help prevent adulteration/contamination incidents
      - Promote use of modern spectrographic methods in monograph *Identification* tests
      - Strengthen USP monographs for OTC drugs
      - Provide appropriate, consistent tests/limits for impurities

# FDA Monograph Modernization Task Group (MMTG)

- May 2010: USP Posts Spreadsheet Lists of "Monographs in Need of Modernization":
  - "Top 200" small molecule monographs (APIs and Drug Products) and "Top 96" excipient monographs
    - Lists comprise high-volume articles
    - Lists note outdated or missing tests/limits
    - Lists track progress of revision
    - Lists updated monthly by USP

# MMTG (continued)

- Oct. 2010: CDER Director Letter to USP:
  - Acknowledges importance of USP's monograph modernization program
  - Requests USP to complete modernization "with urgency"
  - Announces formation of new FDA Task Group to help USP prioritize monographs needing modernization, especially:
    - Drugs/excipients vulnerable to EMA
    - USP monographs for OTC drugs

# MMTG (continued)

- Nov 2010: MMTG chartered under FDA Pharmaceutical Quality Standards Working Group (SWG)
  - Co-chairs: Paul Seo and Larry Ouderkirk
    - Nine (9) other members from CDER, CVM, & ORA
  - Purpose: "…to identify and develop risk-based prioritization schemes to focus on the revision of antiquated, missing, or nonspecific tests in USP and NF monographs…."
  - MMTG to communicate to USP which monograph revisions are of highest priority to FDA, based on potential public health benefit/protection

# MMTG (continued)

- Nov. 2010: MMTG letter to USP listed initial "Top 10" USP/NF Monographs for priority modernization.
  - Special initial emphasis on OTC drugs and widely-used excipients
  - Known impurity issues for certain OTCs
  - Typically, excipients comprise large weight percentage in a drug product formulation

# November 2010 Submission to USP

| Monograph(s) |
| --- |
| Acetaminophen (drug substance) |
| Acetaminophen Oral Suspension; Acetaminophen Oral Solution; Acetaminophen for Effervescent Oral Solution |
| Oral Solution Containing at Least Three of the Following: Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine |
| Acetaminophen, Dextromethorphan Hydrobromide, Doxylamine Succinate, and Pseudoephedrine Hydrochloride Oral Solution |
| Acetaminophen Tablets |
| Acetaminophen Capsules |
| Diphenhydramine Hydrochloride |
| Diphenhydramine and Pseudoephedrine Capsules |
| Povidone; Crospovidone; Copovidone |
| Talc |

# MMTG (continued)

- Following the Nov. 2010 letter, FDA and USP have met to discuss the issues
  - USP has begun work to revise the FDA-identified monographs
  - USP also continues its work to modernize other listed monographs, in addition to those identified by FDA
  - Revisions are tracked on USP's posted lists of small molecule and excipient monographs in need of modernization
- FDA is involved with USP's modernization efforts, as necessary

# Current MMTG Efforts

- FDA will continue to provide periodic lists of highest priority revisions to USP

- FDA plans to implement a risk-based scheme to prioritize USP's Top 200 and Top 96 lists of monographs, as well as to add other monographs, as necessary

# Current MMTG Efforts (continued)

- Risk-based prioritization could consider multiple factors, such as API or drug product, sales volumes, potential for EMA, drug regulatory status, drug therapeutic class
- Model would be refined as necessary as project continues
  - Recently, MMTG conducted internal survey across multiple FDA offices to help identify additional monographs in need of modernization

# Current MMTG Efforts (continued)

- Risk-based prioritization schemes would be separately developed for drug and excipient monographs, but applied in a similar manner
  - For example, sales volume data, EMA potential data
- MMTG plans to send next set of USP/NF priority monographs in the near future

# FDA Monograph Modernization Task Group (MMTG)

**MMTG Co-Chairs:**

Paul Seo, CDER/OPS-IO
Larry Ouderkirk, CDER/OC/OMPQ

**MMTG Members:**

Ali Al-Hakim, CDER/ONDQA
Stephanie Bowman, CVM
Lucinda (Cindy) Buhse, CDER/OPS/OTR
Scott Furness, CDER/OND/ODE-IV
Dennis Guilfoyle, ORA
Frank Holcombe, CDER/OGD
Robert King, CDER/OPS-IO
Donald Lech, CDER/OC/OMPQ
Ian (Paul) Mayers, ORA

# OTC Monographs: Improving Quality Assessment Standards

*Advisory Committee for Pharmaceutical Science*
*and*
*Clinical Pharmacology*

*July 27, 2011*

**Reynold Tan, Ph.D.**
**Interdisciplinary Scientist**
**Division of Nonprescription Regulation Development Office of Drug Evaluation IV**
**Office of New Drugs (OND), CDER, FDA**

# Over-the-Counter (OTC) Drugs

# FDA Regulation of OTC Drugs

Two regulatory processes for all OTC drugs:

1. OTC New Drug Application (NDA)

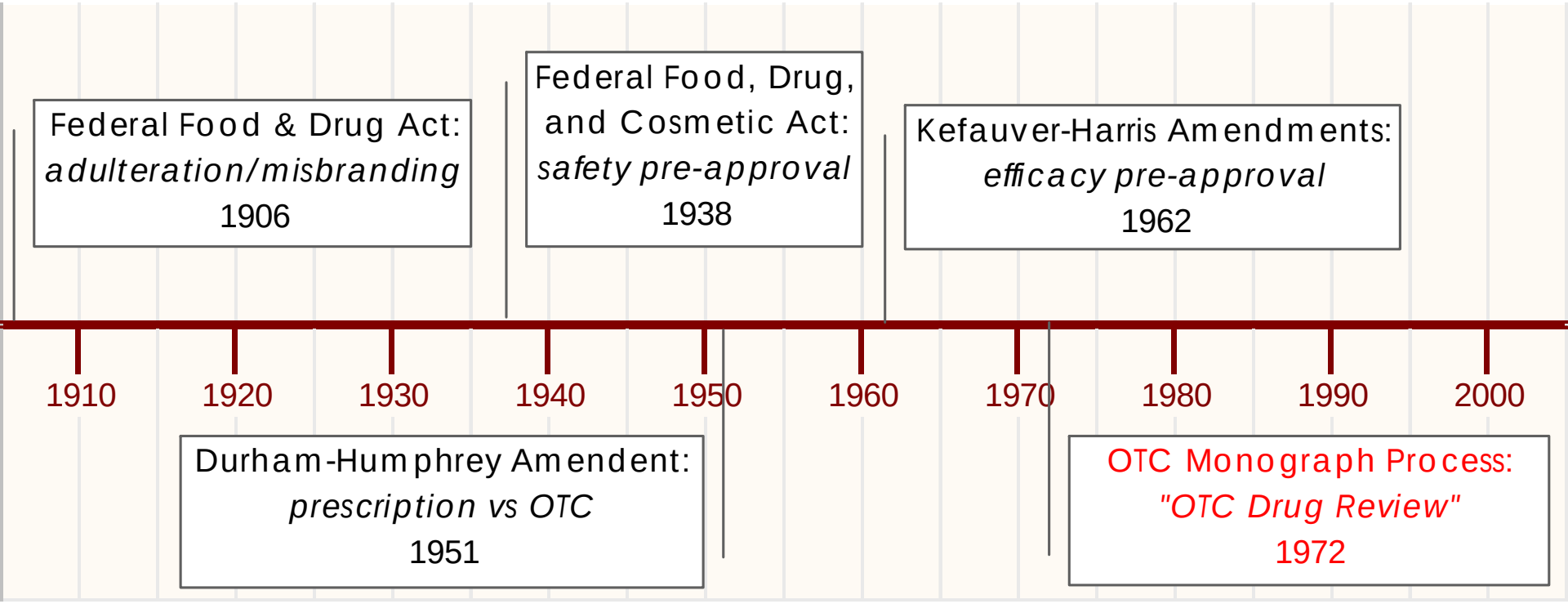
2. OTC Drug Monograph

# Over-the-Counter (OTC) Drugs

*New Drug Application (NDA)*

*OTC Drug Monograph*

# OTC Monograph Process: Creation



# Over-the-Counter (OTC) Drugs

*New Drug Application (NDA)*

*OTC Drug Monograph*

# Creating an OTC Monograph

- Data request
  - industry, healthcare professionals, consumers
- Expert review
  - advisory review panels (e.g., Antacid Panel, Antimicrobial Panel, Dental Panel, Cough/Cold Panel…)
  - public meetings
  - OTC active ingredients classification (21 CFR 330.10):
    - Category I: Generally Recognized as Safe & Effective (GRASE)
    - Category II: Not GRASE
    - Category III: Need more data

# Creating an OTC Monograph (cont.)

Advance Notice of Proposed Rulemaking

Panel

Proposed Rule

("Tentative Final Monograph")

Public

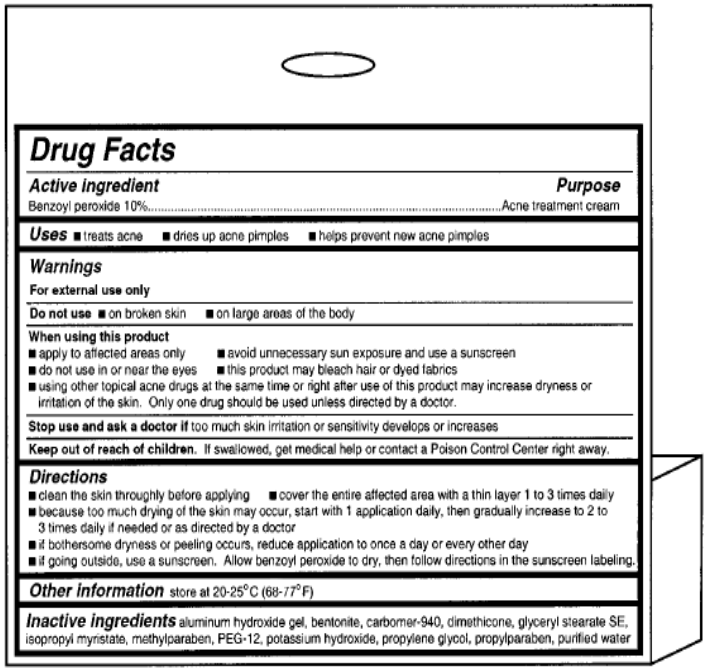
Final Rule

("Final Monograph")

# What's in an OTC Monograph?

## GRASE (Generally Recognized As Safe and Effective)

- Active ingredients
  - dosage strength
  - dosage form
- Labeling requirements
  - indications
  - warning & directions
- Final formulation testing
- Label example



**Drug Facts**

**Active ingredient** — **Purpose**
Benzoyl peroxide 10%.....Acne treatment cream

**Uses** ■ treats acne ■ dries up acne pimples ■ helps prevent new acne pimples

**Warnings**

**For external use only**

**Do not use** ■ on broken skin ■ on large areas of the body

**When using this product**
■ apply to affected areas only ■ avoid unnecessary sun exposure and use a sunscreen
■ do not use in or near the eyes ■ this product may bleach hair or dyed fabrics
■ using other topical acne drugs at the same time or right after use of this product may increase dryness or irritation of the skin. Only one drug should be used unless directed by a doctor.

**Stop use and ask a doctor if** too much skin irritation or sensitivity develops or increases

**Keep out of reach of children.** If swallowed, get medical help or contact a Poison Control Center right away.

**Directions**
■ clean the skin throughly before applying ■ cover the entire affected area with a thin layer 1 to 3 times daily
■ because too much drying of the skin may occur, start with 1 application daily, then gradually increase to 2 to 3 times daily if needed or as directed by a doctor
■ if bothersome dryness or peeling occurs, reduce application to once a day or every other day
■ if going outside, use a sunscreen. Allow benzoyl peroxide to dry, then follow directions in the sunscreen labeling.

**Other information** store at 20-25°C (68-77°F)

**Inactive ingredients** aluminum hydroxide gel, bentonite, carbomer-940, dimethicone, glyceryl stearate SE, isopropyl myristate, methylparaben, PEG-12, potassium hydroxide, propylene glycol, propylparaben, purified water

# Example: OTC Antacid Monograph

§331.10 *Active ingredients*…Calcium, as carbonate or phosphate; maximum daily dosage limit 160mEq. calcium (e.g., 8 grams calcium carbonate)

§331.30(b) *Indications*…‘‘For the relief of’’ (optional, any or all of the following:) ‘‘heartburn,’’ ‘‘sour stomach,’’and/or ‘‘acid indigestion’’

§331.30(c) *Warnings*…‘‘Do not take more than (maximum recommended daily dosage) in a 24–hour period, or use the maximum dosage of this product for more than 2 weeks,

***Drug Facts***

***Active ingredient(s)*** ***Purpose***
Calcium carbonate USP 750mg.....Antacid

***Use(s)*** relieves ▪acid indigestion ▪heartburn ▪sour stomach

***Warnings***
**Ask a doctor or pharmacist before use if you are** taking a prescription drug. Antacids may interact with certain prescription drugs.

**When using this product**
▪do not take more than 10 tablets in 24 hours
▪do not use the maximum dosage for more than 2 weeks

**Keep out of reach of children.** In case of overdose, get medical help or contact a Poison Control Center right away.

***Directions***
chew 2-4 tablets as symptoms occur, or as directed by a doctor

***Other information*** store at room temperature

***Inactive ingredients*** sucrose, corn starch, talc, mineral oil, natural and artificial flavors, adipic acid, sodium polyphosphate, red 40 lake, yellow 6 lake, yellow 5 lake, blue 1 lake

***Questions or comments?*** 1-800-xxx-xxxx

# OTC NDA vs. OTC Monograph

| OTC NDA Process | OTC Monograph Process |
|---|---|
| Pre-market approval | No pre-market approval |
| Drug product-specific | Active ingredient-specific (per OTC drug category) |
| Confidential filing | Public process |

# OTC NDA vs. OTC Monograph: Quality Assessment

| OTC NDA Process | OTC Monograph Process |
|---|---|
| FDA evaluates <u>each product</u> individually for:<br><br>• Drug substance synthesis<br>• Formulation<br>• Analytical methods<br>• Manufacturing & process controls<br>• Stability | FDA evaluates <u>each active ingredient</u>. No product pre-approval.<br><br>• Quality assessment through conformance to corresponding USP monographs |

# OTC Monograph Quality Assessment: USP Monograph Conformance

21 CFR 330.10(a)(2): Inclusion in an OTC drug monograph requires:

- "An official United States Pharmacopeia (USP)-National Formulary (NF) drug monograph for the active ingredients(s),"

- or -

- "a proposed standard for inclusion in an article to be recognized in an official USP-NF drug monograph for the active ingredient(s)"

# OTC NDA vs. OTC Monograph: Consumer Quality Expectations

| OTC NDA Process | OTC Monograph Process |
|---|---|
| | |

# Potential Quality Problems for OTC Monograph Drugs

- Intentional quality failures or economically-motivated adulteration
  - Heparin, Diethylene glycol

- Unintentional quality failures
  - No standard testing for residual solvents, degradation products, analytical methods, drug product formulation, drug substance process impurities

# Impurities Assessment of OTC Monograph Drugs

| OTC Monograph Drug | USP DP Impurity Testing Protocol |
|---|---|
| Acetaminophen | B(2), C(6) |
| Aspirin | B (7) |
| Phenylephrine | B(1) , C(3) |
| Chlorpheniramine | C (4) |
| Brompheniramine | C (2) |
| Guaifenesin | C (3) |
| Dextromethorphan | C (1) |
| Pseudoephedrine | C (4) |
| Methyl Salicylate | C (1) |
| Menthol | C (1) |
| Bisacodyl | C (3) |

A = Adequate
B = Inadequate
C = Does not exist

# Timeline: Addressing the Concern

- Consumer Healthcare Products Association (CHPA) – Manufacturing Controls Seminar; October, 2008
- FDA Working Group (CDER/DNRD/OPS/OC); 2009
  - CDER: Center for Drug Evaluation & Research
  - DNRD: Division of Nonprescription Regulation Development
  - OPS: Office of Pharmaceutical Science
  - OC: Office of Compliance
  - Developed prioritization scheme based on risk
  - Conducted brief survey of marketed OTC drug products
- FDA/OPS approached USP; early 2010
- United States Pharmacopeia (USP) approached CHPA; 2010
- FDA-USP-CHPA Committee; summer 2010

# Timeline: Addressing the Concern (cont.)

- FDA Compendial Monograph Modernization Task Group; fall, 2010
- CDER letter to USP: Prioritize USP monographs to be modernized; November, 2010
  - 15 USP monographs (13 drugs substances/products, 2 excipients)
    - All drugs were OTC monograph drugs containing acetaminophen or diphenhydramine!
- USP letter to FDA: Form expert panels to address priority monographs; December, 2010
  - Acetaminophen Expert Panel – first meeting held 6/23/11
  - Diphenhydramine Expert Panel – to be formed
  - <1086> impurities general chapter Expert Panel – to be formed
- USP symposium on OTC monograph drugs; September, 2011.

# FDA-USP-CHPA Committee

## Modernization of compendial monographs

- USP identified list of 200 small molecules monographs and 96 excipient monographs - published 5/28/2010
  - Updating and/or adding storage conditions
  - Updating assay methodologies (*e.g.*, replacement of a titration method with a modernized validated HPLC method)
  - Replacement of non-specific ID procedures with specific procedures (*e.g.,* IR spectroscopy)
  - Addition of missing procedures for key aspects (*e.g.,* **impurities**)
    - 142 (43%) of the USP prioritized list identified the addition of impurities testing to the pertinent compendial monographs.

# FDA-USP-CHPA Committee (cont.)

## Modernization of compendial monographs

- FDA Compendial Monograph Modernization Task Group
  - Oversee all OTC monograph modernization and prioritization
  - Develop a science- and risk-based approach for ongoing prioritization and oversight of USP monograph modernization efforts
  - Work with USP to achieve the improvements to compendial monographs in accordance with the USP Resolutions adopted for the 2010-2015 cycle
  - Focus ongoing efforts for USP monograph modernization on OTC drugs and excipients whose monographs currently present the greatest risk to public health
  - Provide these recommendations in writing to USP on a regular basis

# OTC Monograph Development: Next Steps

- Short Term
  - FDA Compendial Monograph Modernization Task Group: In collaboration with USP & CHPA, identify & develop science and risk-based prioritization schemes to prioritize USP/NF monographs most in need of modernization.
  - FDA-USP-CHPA Committee: Add and/or modernize appropriate methodology in those prioritized compendial monographs.

- Long Term
  - To address impurities comprehensively, could move informational <1086> to the required chapters below <1000>, with the addition of much of the ICH Q3 specificity.

# For more information:

http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm106368.htm

Reynold.Tan@fda.hhs.gov

U.S. PHARMACOPEIA
The Standard of Quality℠

FDA Pharmaceutical Science and Clinical Pharmacology Advisory Committee
July 27, 2011

# USP Monograph Modernization Initiative – Small Molecules

Karen A. Russo, Ph.D.
Vice President, Small Molecules

# USP Commitment



*April 24, 2010*

## Resolutions Supporting Public Health Adopted by Convention

Strengthen USP's Relationship with the U.S. Food and Drug Administration. USP resolves to strengthen its relationship with the Food and Drug Administration (FDA), and work with FDA and other public and private stakeholders to explore mechanisms to enable USP to provide and maintain up-to-date national standards for legally marketed drugs and excipients in the United States.

# USP Monograph Modernization



- Primary driver is maintaining up-to-date standards to support USP's commitment to public health
- Need for modernization
  - Monographs have been official for several years, decades in some cases
  - Content does not reflect current expectations for procedures and acceptance criteria
  - Complaints from manufacturers
  - General lack of specificity
- Modernization is a subset of USP's ongoing revision work, started using the term "modernization" in 2009

# USP Monograph Modernization



- Benefits
  - Strengthens the public standards
  - Moves from non-specific to specific procedures
  - Considers practical factors
    - removes unnecessary tests
    - Safety/environmental issues such as eliminating use of chlorinated solvents
    - hard to find equipment
  - Increases consistency across monographs

# USP Monograph Modernization



- *USP's greatest challenge is obtaining updated procedures and acceptance criteria—manufacturers are encouraged to submit proposals to USP*
- Pace of monograph modernization is linked to availability of procedures
- FDA's involvement is likely to encourage manufacturers to participate in the modernization efforts

# USP Monograph Modernization



- Recent efforts to increase visibility of the modernization effort
  - Convention resolution (April 2010)
  - Launched monograph modernization web page (May 2010)
  - Working with FDA Monograph Modernization Task Group (MMTG, Nov 2010-ongoing)
  - Launched modernization “hot topics” web page (Feb 2011)
  - USP webinar on modernization (Feb 2011)
  - Presentation at USP Prescription/Nonprescription Stakeholder Forum (May 2011)

# USP Monograph Modernization Process



- Modernization of monographs achieved by
  - *Replacing* outdated procedures (e.g., packed column GC, TLC, wet chemistry tests, etc)
  - *Adding* critical tests to the monograph (e.g., impurities/degradants)
  - *Deleting* non-value added tests, as needed (e.g., odor test, melting point)
- Follows USP's standards-setting process
- Modernization proposals published in PF for a 90-day comment period; accelerated revision process may be used, as needed
- Typical timeline for a complete proposal to reach official status is about two years, depends on many factors

# USP Monograph Modernization Prioritization



- In 2005, USP Scientific Liaisons and Expert Committee members reviewed monographs and noted where modernization was needed
- Work proceeded as monograph revisions, not a formal initiative
- In 2009-2010, information was compiled into a master list and prioritized
- Prioritization values determined by factors such as therapeutic category and extent of USP reference standard use
- 700+ small molecule monographs included in master list, not an exhaustive list of all monograph issues
- A portion of the master list – the “Top 200” list – was posted on USP web site in May 2010 as a call for procedures
  - http://www.usp.org/USPNF/submitMonograph/improveMon.html
  - List is updated monthly to show progress (e.g., proposals received, etc)

# USP Monograph Modernization Major Categories



- *No impurity test*
- Non-specific Identification procedures
- Non-specific Assay procedures
- Outdated procedures
  - Packed column GC procedures
  - TLC (particularly <466> Ordinary Impurities), UV, or wet chemistry test for impurities
- Safety-related concerns (e.g., use of chlorinated solvents, mercury salts)

# USP Monograph Modernization Scope



From the Top 200 list

- Major categories accounting for about 93% of the entries
  - Missing impurities test
  - Assay by titration
  - Procedures using TLC, packed GC columns, UV
- Majority of the work (>90%) has not started
- Exploring options for improving efficiency and impact
  - Working on monograph families rather than individual monographs (e.g., acetaminophen)
  - Drug substance vs dosage forms
  - Address by technique (e.g., replace all packed column procedures, etc)
  - Combination of these options likely
- USP welcomes recommendations from MMTG to refine prioritization

# USP Monograph Modernization Progress



Over the past two fiscal years (July 2009-July 2011)

- Submitted 314 monograph revision proposals in PF
- Of these, 76 (24%) are monograph modernization proposals

Work in Progress (not published in PF yet)

- 71 monographs with active modernization work
  - 36 (51%) proposals from manufacturers
  - 35 (49%) proposals USP-initiated (USP lab)

# Monograph Modernization: Recent Examples



| Monograph | PF Citation | Modernization |
|---|---|---|
| Alclometasone Dipropionate | PF 36(5) [Sep-Oct 2010] | Replace Ordinary Impurities by TLC with HPLC |
| Glycopyrrolate | PF 37(1) [Jan-Feb 2011] | Replace titration Assay with HPLC; replace Ordinary Impurities by TLC with HPLC; delete Melting Range or Temperature test; add test for Limit of Erythro Isomer by HPLC |
| Glycopyrrolate Tablets | PF 37(1) [Jan-Feb 2011] | Replace UV-based Assay and Dissolution procedure with HPLC; add impurities test |
| Spironolactone | PF 37(1) [Jan-Feb 2011] | Replace choloroform with alcohol in Specific Rotation test; replace <197S> using chloroform with <197K |
| Temazepam | PF 36(6) [Nov-Dec 2010] | Replace TLC-based impurities procedure with HPLC procedures; removed use of Internal Standard from the Assay |

# FDA Priority Monographs



- Nov 16, 2010 letter to USP from the FDA Monograph Modernization Task Group (MMTG)
- Requested modernization of Acetaminophen and Diphenhydramine monographs
  - Modernization effort applies to Acetaminophen and Diphenhydramine drug substances and their related dosage form monographs (collectively known as the monograph “families”)
  - Single and multi-active ingredient OTC (primarily) and Rx products
  - Primary issue of concern is missing impurity/degradant tests
  - Revisions to other monograph test(s) and procedure(s) may be needed

# FDA Priority Monographs: Progress



- Acetaminophen
  - Family of 37 monographs
  - FDA requested addition of a test(s) for the nephrotoxic impurity *p*-aminophenol (PAP) and degradants in all dosage form monographs

- Acetaminophen Expert Panel
  - Formed in May 2011
  - Includes representatives from FDA, industry and Expert Committees
  - Scope includes the Acetaminophen monograph family
  - PAP limits recommended by FDA
    - 0.15% for oral liquid dosage forms
    - 0.01% for solid oral dosage forms

# FDA Priority Monographs: Progress



- Acetaminophen drug substance monograph
  - Extensive revisions needed
  - Lab work in progress at USP for PAP procedure and Assay
  - No change to current PAP limit expected (50 ppm)
  - Anticipate publication of a proposal in PF in early 2012 (may be available on the USP web site in advance of PF)

- Acetaminophen dosage form monographs
  - Need to determine procedure(s) suitable for PAP and possibly other degradants
  - USP plans to start lab work in September 2011
  - Anticipate drafting a chapter for determination of PAP and other degradants that can be cited in all acetaminophen dosage form monographs

# FDA Priority Monographs: Progress



- Diphenhydramine
  - Family of 8 monographs
  - General impurities procedures to be added/revised
- Diphenhydramine Hydrochloride drug substance monograph
  - Modernization proposal published in PF 37(3) [May-June 2011]
  - Comment period ends July 31, 2011
  - Impurities test added (based on EP monograph)

# FDA Priority Monographs: Progress



- Diphenhydramine Citrate drug substance monograph
  - USP is planning lab work to verify if Diphenhydramine Hydrochloride impurities procedure will work for the Citrate
  - Publication of proposal in PF to be determined

- Diphenhydramine dosage form monographs
  - Plan to add impurities test, anticipate lab work will be needed
  - Publication of proposals in PF to be determined

# Current Activities



- Ongoing work to revise FDA priority monographs
- Collaborations with the MMTG and CHPA
- Working with manufacturers/sponsors of individual modernization proposals
- Expert Committee and Expert Panel involvement and awareness
  - Modernization is included in the Work Plan for each of the four Small Molecule Monographs Expert Committees
- About 70 monographs with modernization proposals in progress

# Moving Forward



- USP efforts
  - Reviewing options for optimizing prioritization and efficiency of work
  - Sourcing procedures from other compendia, literature, other
  - USP will continue to use its lab resources
  - Form Expert Panels, as needed, to address specific topics
- Collaboration
  - Explore possible lab support from CRADA with the FDA
  - Collaborate with FDA MMTG, refine priorities as needed
  - Engage CHPA and other interested parties

# Moving Forward



- Communication and outreach
  - "Design phase" approach bringing together manufacturers, regulators, and stakeholders
    - Web meetings
    - Public forums
    - Workshops
  - Update the USP Monograph Modernization web page monthly
  - Maintain the Modernization Hot Topics page
    - For updates to high profile issues (e.g, FDA priority monographs)
    - http://www.usp.org/hottopics/monographs.html
  - Update progress on Expert Committee Work Plans (posted on USP web site at specified intervals)

# Upcoming Events



- USP OTC Workshop September 8-9, 2011
  - September 8-9, 2011, USP headquarters, Rockville, MD
  - Co-sponsored by FDA
  - Modernization activities to be discussed
    - Updates for FDA priority monographs
    - http://www.usp.org/meetings/asMeetingIntl/rockvilleEvent.html
- CHPA Product Quality and Operations Workshop
  - October 6-7, 2011
  - USP is a co-sponsor

# Conclusions



- Monograph Modernization is a major initiative in the USP 2010-2015 revision cycle
- USP is devoting significant resources to this effort
- Collaboration with FDA, industry and other stakeholders is key to advancing the work
- With FDA involvement in prioritizing and requesting submissions, industry is much more likely to come to the table
- Long-term goal is to implement a regular monograph review process to monitor the needs for further modernization

# Contact Information



Karen A. Russo, Ph.D.
Vice President, Small Molecules
kar@usp.org

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# *Thank You*

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FDA Pharmaceutical Science and Clinical Pharmacology Advisory Committee
July 27, 2011

# USP Monograph Modernization Initiative – Excipients

Catherine M. Sheehan, M.S.
Director, Excipients

# Excipient Monograph Modernization: Major Categories



| Excipient Monograph Modernization: Major Categories | **Total** |
|---|---|
| No Identification (ID) or non-specific ID procedures | 98 |
| No Assay | 27 |
| Non-specific assay (titration, etc) | 52 |
| Outdated procedures: Packed column GC/TLC/UV, or wet chemistry test for impurities | 25 |
| No impurity tests (organic and inorganic) | 2 |

–Majority of the work (about 95%) is to be done

# Excipient Monograph revisions and modernizations since 2005



## USP 29-NF 24-2S:

- Microcrystalline Cellulose
- Powdered Cellulose
- Hydroxypropyl Cellulose
- Sodium Starch Glycolate
- Sodium Starch Glycolate
- ***Sesame oil***

## USP 30-NF 25-2S:

- ***Almond Oil***

## USP 31-NF 26-2S:

- ***Glycerin***
- Poloxamer
- Mineral Oil
- Light Mineral Oil
- Rectal Mineral Oil
- Topical Light Mineral Oil
- Paraffin

## USP 32-NF 27:

- Acetone
- Butylated Hydroxytoluene
- Methyl alcohol

## USP 32-NF 27-1S:

- Amino Methacrylate Copolymer
- Betadex
- Alfadex
- Polyvinyl Alcohol
- Liquid Glucose
- Lecithin

## USP 32-NF 27-2S:

- Xylose
- Benzalkonium Chloride
- Caprylocaproyl Polyoxylglycerides
- Lanolin Alcohol
- Linoleoyl Polyoxylglycerides
- Oleoyl Polyoxylglycerides
- ***Soybean Oil***
- ***Corn Oil***
- ***Cottonseed Oil***
- Lauroyl Polyoxylglycerides
- Stearoyl Polyoxylglycerides

## USP 33-NF 28:

- *Peanut Oil*
- *Olive Oil*
- Methacrylic Acid Copolymer Dispersion
- Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion

## USP 33-NF 28-1S:

- Pectin
- Fumaric acid

## USP 33-NF 28-2S:

- Polydextrose
- Tartaric acid
- Amylene hydrate

## USP 33-NF 28 Reissue-1S:

- ***Propylene Glycol***
- ***Sorbitol Solution***
- ***Sorbitol sorbitan solution***
- ***Noncrystallizing Sorbitol Solution***

## USP 34-NF 29:

- ***Maltitol solution***
- Benzalkonium Chloride
- Benzalkonium Chloride Solution
- Polyethylene Oxide
- Polyoxyl Stearyl Ether
- Butylated Hydroxyanisole

## USP 34-NF 29-1S:

- Succinic Acid
- Ascorbyl Palmitate

## USP 34-NF 29-2S:

- Maleic Acid
- Sorbic Acid
- Polyoxyl Lauryl Ether
- Povidone
- Crospovidone

## USP 35-NF 30:

- Agar
- Ammonio Methacrylate Copolymer
- Zein
- Sucrose
- Stearic acid
- Magnesium stearate
- ***Hydrogenated starch hydrolysate***

# Revisions/Modernizations of *USP-NF* Fixed Oil Monographs since 2005



| Recent *USP-NF* Fixed Oil Monograph Revisions/Modernizations | Publication |
|---|---|
| *NF* Sesame Oil | *USP29-NF24* 2S [2006] |
| *NF* Almond Oil | *USP30-NF25* 2S [2007] |
| *USP* Soybean Oil | *USP32-NF27* 2S [2009] |
| *NF* Corn Oil | *USP32-NF27* 2S [2009] |
| *NF* Cottonseed Oil | *USP32-NF27* 2S [2009] |
| *NF* Peanut Oil | *USP33-NF28 Reissue* [2010] |
| *NF* Olive Oil | *USP33-NF28* Reissue [2010] |

**Result of Collaboration with Industry - Revised Standards Protect Patients from Adulterated Excipients**

# Revisions of Fixed Oil Monographs



- Helps protect against economically motivated adulteration (EMA)
- Assures the Identity, Strenght, Quality and Purity of substance
- Fixed oils are expensive and prone to substitution with cheaper oils
  - e.g., a mixture of almond oil and persic oil (1:1) would pass the Almond oil *NF* 23 monograph
- "Value added specific tests" included:
  - *Identification*: Add a Fatty acid composition test that assures adequate purity
  - *Impurities*: controls residues due to its origin, refining steps or residual catalysts
  - *Peroxide value*: indicates primary oxidation products and stability of oil
  - *Acid Value*: accesses free fatty acids, an indicator for hydrolytic status of oil product
  - *Labeling*: indicates presence of additives and if suitable for eg., injectable dosage forms
  - *Sterol Composition:* reveals the identity of the components in a mixture
  - *Fatty acid composition:* composition profile of individual fatty acids

# Revision of *NF* Olive Oil Monograph



| *NF* 23 Almond Oil | Revision | *NF* 25 2S Almond Oil |
|---|---|---|
| No Identification | Fatty acid composition (FAC) provides composition profile of individual fatty acids | **Identification**— It meets the requirements of the test for **Fatty acid composition** |
| No Assay | Fatty acid composition serves as assay | **Fatty acid composition** |
| No Labeling | Indicates use of additives | **Labeling** |
| Foreign Kern oils | Deleted | |
| Cottonseed oil | Deleted | |
| Sesame oil | Deleted | *Non value added procedures with* |
| Mineral oil and Foreign fatty oils | Deleted | *outdated technologies were* |
| Foreign oils | Deleted | *replaced with specific updated* |
| Free fatty acid <401> | Deleted | *analytical procedures* |
| Iodine value <401> | Deleted | |
| Saponification value <401> [unnecessary test if *FAC* is available; estimated from the *FAC*] | Deleted | |
| | Indicates primary oxidation products, an indicator of stability of oil product | **Peroxide test** |
| | Sterols are very specific for each oil source. Test reveal the identity of the components in a mixture. Found in almost all fats and oils. Controlling identity and quality of the oils | **Sterol composition** |

# USP Glycerin Monograph



- In the late 1990s, in response to the Haiti incident, USP revised the Glycerin monograph to include:
  - Identification section: Addition of “Identification Test B”. Glycerin Identification by retention time
  - Impurities section: Addition of the “*Limit of DEG and Related Compounds”* Test
    - A capillary gas-chromatographic (GC) method with flame ionization detection (FID)
    - NMT 0.1% DEG

# History of adulteration with Diethylene Glycol



| Country | Year | Incident |
|---|---|---|
| USA | 1937 | "Elixir sulfanilamide" – 107 deaths<br>*Resulted in the implementation of the1938 Amendment to the FFD&C Act* |
| South Africa | 1969 | Sedative formulated with DEG – 7 deaths |
| Italy | 1985 | DEG in wines from Austria – no known deaths |
| India | 1986 | Medicinal glycerin laced with DEG – 14 deaths |
| Nigeria | 1990 | Acetaminophen syrup containing DEG – 40 deaths (some sources say 200 deaths) |
| Bangladesh | 1990-2 | Acetaminophen syrup containing DEG – 339 deaths |
| Haiti | 1995/6 | Cough medicine containing DEG – 85 deaths |
| Panama | 2006 | Cough and anti-allergy syrup containing DEG – 46 deaths (116 or 365 according to other sources) |
| USA | 2006/7 | Toothpaste containing DEG – no deaths |
| Panama | 2007 | Toothpaste containing DEG – no deaths reported |
| Nigeria | 2008/9 | Teething formula contaminated with DEG from propylene glycol – 84 deaths |
| Bangladesh | 2009 | Paracetamol syrup to children adulterated with diethylene glycol. Twenty-four children reported dead |

# FDA request



- **April 2007:** FDA request USP to modernize the Glycerin Identification section to include the identification and quantitation of Diethylene glycol (DEG) in glycerin.
- **Jan. 2009:** FDA letter requested modernization of both Sorbitol Solution and Propylene Glycol consistent with the update to the USP Glycerin Monograph
- **Rationale:** GMPs allow the use of Identification testing alone, by dosage form manufacturers, for raw material(s) qualification
  - manufacturers could therefore not deviate from the DEG limit since this would be an aspect of identity.
- **Challenge:** Complex issue relating to 'requirement' that contaminant/adulterant be considered part of an article's Identification
- **Concurrently:** Industry submitted a GC method to detect ethylene glycol (EG) in a request for revision to *USP-NF* sugar alcohol monographs and indicated that EG is a process impurity.
  - This request arose because Residual Solvents <467> did not have a test method for EG.
  - FDA agreed to the inclusion of EG in the Identification Test for "high priority" monographs.

# FDA "High Priority" Monograph Revisions for Limit of DEG and EG



- **Glycerin**
  - Official date **May 1, 2009 (*USP* 31-*NF* 26-2S)**

- **Sorbitol Sorbitol Solution**
- **Sorbitan solution**
- **Noncrystallizing sorbitol solution**
- **Propylene glycol**
  - Official date **February 1, 2010 (*USP*33-*NF*28 Reissue-1S)**
- **Maltitol Solution**
  - Official date **August 1, 2010** (***USP* 34-*NF* 29**)

- **Hydrogenated Starch Hydrolysate (*USP* 35-*NF* 30)**

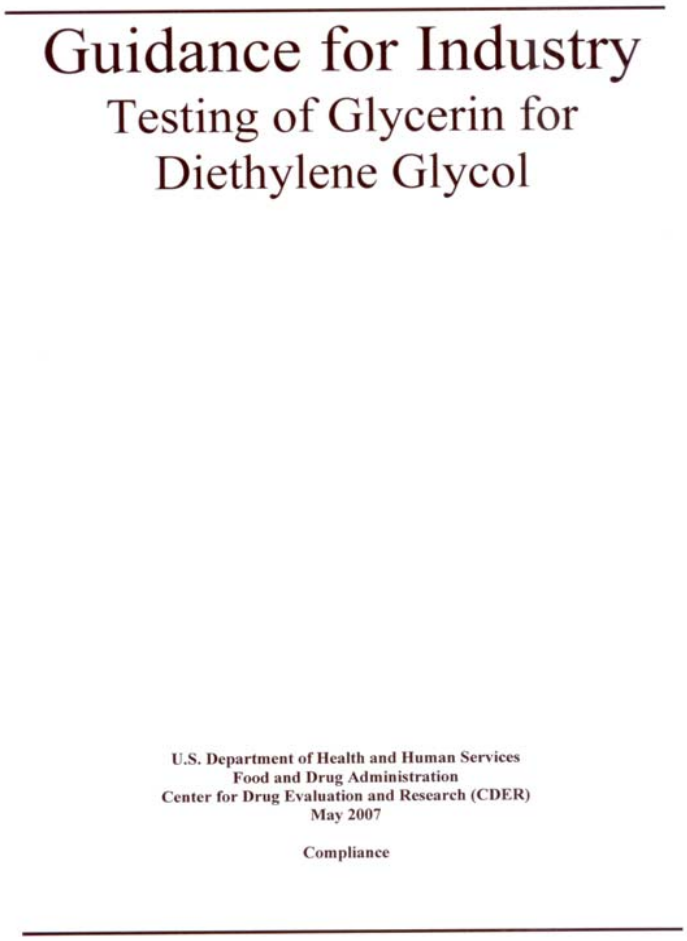
# FDA "High Priority" Monograph Revisions for Limit of DEG and EG



FDA Guidance 2007–

- Perform a specific identity test that includes a limit test for DEG per cGMPs (NMT 0.10%).
- Reliance on COA is not sufficient to ensure quality of glycerin
- Recommends intimate knowledge of the supply chain

- As a result of collaboration with FDA and stakeholders, USP Lab. developed capillary gas chromatographic methods with FID and validated for analyzing EG and DEG (NMT 0.10%).


Guidance for Industry

Testing of Glycerin for Diethylene Glycol

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
May 2007

Compliance

# FDA Priority Monographs



- High priority monographs identified by FDA in Nov. 16, 2010 letter
- Includes USP and NF excipient monographs in Pharmacopeial Discussion Group* (PDG) work program
  - USP Talc, USP Povidone, NF Crospovidone, NF Copovidone

USP's Challenges for PDG related excipient monographs

- Obtaining procedures and acceptance criteria
- With FDA involvement in prioritizing and requesting submissions, industry is much more likely to come to the table
- *Manufacturers are encouraged to submit proposals to USP*
- Need to coordinate with members of the Pharmacopeial Discussion Group as these monographs are within the PDG work program. Members are European Pharmacopoeia (EP), Japanese Pharmacopoeia (JP) and USP.

*Information on the Pharmacopeial Discussion Group available at

http://www.usp.org/USPNF/pharmacopeialHarmonization/

# FDA Priority Monographs



- FDA MMTG revisions requested:
- USP Povidone, NF Crospovidone, NF Copovidone:
  - 3 Povidones not consistent w.r.t. impurity specifications. Should be harmonized within USP and to the EP monographs (Limit of Hydrazine; Limit of aldehydes; Peroxides; Heavy metals.
  - Nitrogen assay test is non specific. Prefer a more specific method due to concerns about economically motivated adulterants, eg., melamine

- USP Talc:
- Labeling statement should be revised to match the statement from the FCC monograph's description thereby assuring that Talc is not sourced from mines that are known to contain asbestos.
- USP should consider revising the current test for *Absence of asbestos* to ensure adequate specificity.

# FDA Priority Monographs: progress



- Povidone
  - PDG Stage 6 adoption includes the addition of tests for
    - Limit of hydrazine
    - Limit of aldehydes
    - Peroxides
  - Posted on harmonization website on Feb. 25, 2011, Official Dec. 1, 2011 (Second Supplement to USP 34–NF 29)

- Crospovidone
  - PDG Stage 6 adoption includes the addition of tests for
    - Peroxides
    - Limit of monomers (vinylpyrrolidinone)
  - Posted on harmonization website on Feb. 25, 2011, Official Dec. 1, 2011 (Second Supplement to USP 34–NF 29)

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# Pharmacopeial Harmonization

## Pharmacopeial Harmonization

USP participates in the Pharmacopeial Discussion Group (PDG), formed in 1989 with representatives of the European Department for the Quality of Medicine in the Council of Europe and the Japanese Pharmacopeia in the Ministry of Health and Welfare (now the Ministry of Health, Labor, and Welfare). PDG meets twice yearly to work on pharmacopeial harmonization topics. In May 2001, PDG welcomed the World Health Organization as an observer. While not part of the International Conference on Harmonization (ICH), PDG usually meets in conjunction with ICH and provides the ICH Steering Committee with reports of its progress.

## Notices of Stage 6 Harmonized Text

USP versions of Stage 6 Harmonized texts, which formerly were published in Pharmacopeial Forum, now appear in this area of the USP Web site. Stage 6 Harmonization includes monographs or general chapters that have completed stages 1-5 of the pharmacopeial harmonization process resulting in an approved global text, and are in the process of adoption by the respective pharmacopeias in their regional style. Stage 6 adopted text is published here so that USP-NF users may become aware of its availability as a pharmacopeial standard and its targeted official date.

## New

- <711> Dissolution (posted 25-Feb-2011; official 01-Dec-2011)
- <905> Uniformity of Dosage Units (posted 25-Feb-2011; official 01-Dec-2011)
- Crospovidone (posted 25-Feb-2011; official 01-Dec-2011)
- Povidone (posted 25-Feb-2011; official 01-Dec-2011)

Next posting date: April 29, 2011

## PDG Harmonization Stages

The specific stages of the PDG Working Procedure (Process) are:

**Stage 1: Identification** The PDG identifies items to be harmonized and designates a coordinating pharmacopeia for each item. The PDG distributes the work by consensus among the three participating pharmacopeias. Harmonization may be carried out retrospectively for existing monographs or chapters, or prospectively for new monographs or chapters.

**Stage 2: Investigation** The investigation process conducted by the coordinating pharmacopeia results in the preparation of a Stage 3 draft monograph or chapter accompanied by a report giving the rationale for the proposal and including validation data where appropriate. This report is based on input that comes from users, authorities, producers, associations, literature, experts, and staff.

**Stage 3: Proposal** The Stage 3 draft is reviewed and commented on by the other two pharmacopeias and their Expert Committees. The coordinating pharmacopeia reviews those comments, prepares a Stage 4 draft, and sends it to the other participating pharmacopeias.

**Stage 4: Official Inquiry** The Stage 4 draft is published for public comment in the Forum of each pharmacopeia. In *PF*, this stage appears as OFFICIAL INQUIRY STAGE 4 in the *Harmonization* section. Each pharmacopeia analyzes the comments it receives and submits the

What's New

PHARMACOPEIAL FORUM
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Click here for details

Call for Candidates: USP Expert Panel on Use of Enzymes in the Dissolution Testing of Gelatin Capsules (04/15/2011)

Dietary Supplements Stakeholder Forum Date Announced (04/12/2011)

Call for Candidates: USP Expert Panel on Beta-alanine (04/06/2011)

Call for Candidates: USP Expert Panel on Measurement of Residual DNA in Biotechnology-Derived Products (04/06/2011)

Call for Candidates: USP Expert Panel on Total Protein Measurement of Biotechnology-Derived Products (04/06/2011)

Prescription/Nonprescription Stakeholder Forum Date Announced (04/06/2011)

Call for Candidates: USP Expert Panel on Talc (04/01/2011)

Vasopressin: Notice of Intent to Revise (03/31/11)

Maltitol Solution Revision Bulletin updated (03/31/11)

Call for Candidates: USP Expert Panel on Acetaminophen (03/22/2011)

Ethylcellulose: Notice of Intent to Revise (03/01/2011)

# FDA Priority Monographs: Progress

## Copovidone: PDG Stage 4

- *PF* proposal published in *PF* 37(4) [July – Aug. 2011]
- Addition of
  - Test for Lead
- Revision of
  - Limit of Monomers (change from titration,(0.1%) to HPLC (0.001%)
- Notice of *Intent to revise* to be posted on the USP website to announce this *PF* proposal
- Scheduled for ***USP* 35-*NF* 30-2S** publication

# FDA Priority Monographs: Progress



- Joint Talc Expert Panel (EP)established May 30, 2011
  - Excipent Monograph Expert Committee (EC)(lead Expert committee) with Physical Analysis Expert Committee.
  - FDA liaison to Talc EP
    - Kick-off telecon meeting held June 21, 2011
    - Second telecon meeting on Aug 15, 2011

Scope:

- Update USP Talc labeling statement to indicate "*Talc is not derived from deposits that are known to contain associated asbestos*" consistent with statements in Talc FCC monograph.
- Based on positive stakeholder comments EC posted the revision via an accelerated revision proposal prior to EP formation

- Current methods for *Absence of asbestos* test are not specific
  - Talc EP to evaluate existing Asbestos methods in USP and offering potential alternative analytical methods and procedures.

# FDA Priority Monographs: Progress



- Revision Bulletin posted, May 1, 2011, official, August 1, 2011
  - To immediately address the Labeling section to include:
  - **LABELING: The label states, where applicable, that the substance** is suitable for oral or topical administration. The certificate of analysis states the absence of asbestos. It also indicates • *that Talc is not derived from deposits that are known to contain associated asbestos, and*• (RB 1-Aug-2011) which method specified in the test for *Absence of Asbestos was used for analysis.*

# FDA Priority Monographs: Progress



- Further discussion with Talc manufacturers revealed significant challenges to the implementation of the proposed FCC statement in the labeling of the USP Talc monograph.
  - Reasons:
  - Absence of clear definitions for talc “deposits”
  - Differences in regulatory expectations between statements in the labeling section of *USP-NF* (mandatory compliance) versus a statement in the Description of the FCC monograph (non-mandatory).
- As a result, USP received a *Request for Postponement* of the Talc Revision Bulletin.
  - Based on discussions with FDA, it was agreed that the final language and placement of the proposed statement would be best handled by the Talc EP.
- Excipients Expert Committee voted in favor of postponing the Talc Revision Bulletin.
- The updated Revision Bulletin was posted on June 30, 2011.

# Current Activities



- **Povidone/Crospovidone/Copovidone**
  - Ongoing work on replacement of nonspecific Nitrogen assay test (<461> Nitrogen Determination (by Kjeldahl method)).
    - FDA prefer a more specific assay due to concerns about EMA involving melamine.
    - Current method is a non specific assay method.
  - Working with experts from industry and stakeholders to look at other possible methodologies to detect potential EMA adulterants.

# Current Activities



- Talc Expert Panel working on a revised version of the originally proposed FCC Description statement to address the Labeling section of the USP Talc monograph.
- Talc EP to evaluate existing Asbestos methods in USP and offering potential alternative analytical methods and procedures.

- Next meeting: August 15, 2011

# Current Activities



- Ongoing work with Povidones and Talc monographs
- Collaboration with the MMTG, industry and stakeholders
- Working with manufacturers/sponsors of individual modernization proposals
- Expert Committee and Expert Panel involvement and awareness
  - Talc Expert Panel formed in May 2011
  - Modernization is included in the Work Plan for Excipient Monographs Expert Committees
- About 6 monographs with modernization proposals in progress

# Current Activities



- Communication
  - Update the USP Monograph Modernization web page monthly
    - Indicate activity on the “Top 96” excipients listed as proposals received
  - Maintain the Modernization Hot Topics page
      - For updates to high profile issues (e.g, FDA priority monographs)
  - Update progress on Expert Committee Work Plans (posted on USP web site)

# Monograph Modernization Strategy and Approaches



- USP's key strategy and approaches for modernization includes:
- Communication and Outreach
  - This involves a "Design phase" approach bringing together manufacturers, regulators, and stakeholders.
  - Web meetings, Public forums, conferences and meetings, Work Shops, Stimuli Articles
  - Use USP Web site for Hot Topics pages and initiative-specific content
  - Pre-publication of high-impact revisions on Web site in advance of PF publication
- Establish relevant Expert Panels
- Conduct relevant workshops

# Conclusion



- Excipient monograph modernization is a major initiative in the 2010-2015 revision cycle
- USP is devoting resources to this effort
- Collaboration with FDA, industry and other stakeholders is key to advancing the work
- Long-term goal is to implement a regular monograph review process to monitor the needs for further modernization

- USP's Challenges
  - Obtaining procedures and acceptance criteria
  - With FDA involvement in prioritizing and requesting submissions, industry is much more likely to come to the table
  - *Manufacturers are encouraged to submit proposals to USP*

# Questions

# USP Contact Information



Catherine Sheehan, M.S.

Director, Excipients

cxs@usp.org

*July 27, 2011*

Consumer Healthcare Products Association

# USP Monograph Modernization:
## The OTC Industry Initiatives

Rachael Carlisle Roehrig, Ph.D.

Director, Technical & Scientific Affairs

Consumer Healthcare Products Association (CHPA)

# CHPA is Commitment to USP Modernization

- Taking a leading role
- Advocating for continual improvement
- Driving science- and risked-based discussions
- Working with USP and FDA
- Moving forward as an aligned industry

# Agenda

USP Monograph Modernization Timeline

CHPA Commitment Letter

CHPA  Activities and Progress

Future Activities

Concluding Points

# Timeline of Events

| | |
|---|---|
| ***May 2010*** | USP posts Monographs in Need of Modernization |
| ***August 2010*** | FDA/USP/CHPA Planning Committee meets |
| ***November 2010*** | FDA prioritizes USP monographs |
| ***January 2011*** | CHPA sends commitment letter |
| ***February 2011*** | USP hosts webinar |
| ***March 2011*** | CHPA forms expert working groups |
| ***June 2011*** | CHPA submits monograph revisions for diphenhydramine |
| ***July 2011*** | CHPA proposes limits for acetaminophen degradant |

# Proposed FDA Role

- Identify and prioritize OTC drug substances or products
- Provide transparency
- Provide continued insight

# Proposed USP Role

- Use existing or novel approaches
- Form expert panels comprised of subject matter experts
- Provide full public review

# CHPA's Commitments

- Maintain high-quality standards
- Provide industry experts
- Establish working groups
- Base efforts on FDA's "prioritization list"
  - Acetaminophen
  - Diphenhydramine
- Propose data-based limits where needed

# CHPA Acetaminophen Degradant Working Group

Bayer Healthcare

Covidien

GlaxoSmithKline Consumer Healthcare

McNeil Consumer Healthcare

Novartis Consumer Health

Perrigo Company

The Procter & Gamble Company

# CHPA Acetaminophen Degradant Working Group - Progress

- Taking a leading role in specifying limits
  - 4-aminophenol
- Analysis of shared information
  - Stability data
  - Safety studies
  - Process capabilities
- Scientifically based outcomes

# CHPA Acetaminophen Degradant Working Group - Progress

- Proposed limits
  - All acetaminophen OTC compendial dosage forms
- Considered criteria
  - Safety profile
  - Available data
  - International guidelines
  - Multiple Pharmacopeias

# CHPA Diphenhydramine Degradant Working Group

- Bayer Healthcare
- Chattem
- GlaxoSmithKline Consumer Healthcare
- McNeil Consumer Healthcare
- Novartis Consumer Health
- Perrigo Company
- Pfizer Consumer Healthcare

# CHPA Diphenhydramine Degradant Working Group - Progress

- Hydrochloride and citrate drug substances
- Collecting and sharing information
  - Process capabilities
  - Analysis of safety studies

# Future Collective Activities

***September 2011***

USP OTC Workshop

- FDA and CHPA plan and participate

*usp.org*

***October 2011***

CHPA's Product Quality & Operations Workshop

- FDA and USP plan and participate

*chpa-info.org*

# Concluding Points

- Continue to provide highest quality medicines to consumers
- Promote compendial harmonization
- Base decisions on risk assessment and science
- Work collaboratively and be transparent

# FDA/USP Science Collaboration

*Advisory Committee for Pharmaceutical Science*
*and*
*Clinical Pharmacology*

*July 27, 2011*

**Jon Clark**

**Associate Director for Program Policy**

**OPS/CDER/FDA**

# Two Projects

Cooperative Research and Development Agreement (CRADA)

- FDA/ORA and USP
- Reference Standard Candidate Assessments
- Monograph Updates
- Economic Adulteration

- Pharmacy Compounding Monographs
  - Measure the Regulatory Suitability

# CRADA Reference Standard

- Controlled substances
- FDA test reference standard candidates
- Approximately 40 candidates each year
- First assessments are under way

# CRADA Monograph Updates

- FDA to provide laboratory support for monograph modernization program
- Coordination
  - USP Laboratories
  - FDA Monograph Modernization Task Group
- In the planning stages

# CRADA Economic Adulteration

- Focus on new technology
  - Portable Devices
- Screen testing for contamination/adulteration
  - Targeting API's and Dietary Supplements
- Coordinating USP, MMTG, Enforcement

# Pharmacy Compounding Monographs

- Compound products according to the Monograph
- Conduct analysis according to the Monograph
- Assess whether the Monograph is suitable for regulatory enforcement

# Roles

- USP prepares the compounded product
- FDA/ORA conducts analysis
- FDA/CDER/ and FDA/ORA conducts assessment
- Timing is sensitive in order to complete analysis before expiration of the compounded product

# Scale of Project

- Propylthiouracil Oral Suspension (OS)
- Pyrazinamide OS
- Ursodiol OS
- Rifabutin OS
- Tacrolimus OS
- Temozolomide OS
- Pentoxifylline OS
- Sironolactone OS
- Sodium Phenylbutyrate OS
- Lamotrigine OS

# Status

- 9 of 10 are compounded and delivered to FDA laboratories
  - Thank You USP!
- 1 of 10 is underway at NIH compounding Laboratory
  - Thank You NIH!
- Intent is to make results public

# Next Steps

- Collaboration between FDA and USP is broad based and continuing
  - Standards updates
  - Laboratory collaboration
- Common interests between USP and FDA result in productive cooperation
- Collaboration is on-going and will be fruitful into the future